The Pennsylvania State University
The Graduate School
Department of Chemistry

DEVELOPMENT AND APPLICATIONS OF PHOSPHORUS LIGANDS IN
RHODIUM-CATALYZED HYDROFORMYLATION AND HYDROGENATION

A Dissertation in
Chemistry
by
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Submitted in Partial Fulfillment
of the Requirements
for the Degree of

Doctor of Philosophy

May 2011
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ABSTRACT

Transition metal-catalyzed homogeneous catalysis is one of the key tools of modern synthetic chemistry. Generally, variation of the steric bulk and electronic properties of the ligands is one of the most efficient methods to improve catalytic performance of an organometallic complex. This dissertation mainly focuses on the design and synthesis of efficient phosphorus ligands and the exploration of their applications in rhodium-catalyzed hydroformylation and asymmetric hydrogenation.

Asymmetric hydroformylation has attracted much attention as an atom economic method to convert olefins into enantiomerically pure aldehydes. Although a number of chiral phosphorus ligands have been developed for this challenging transformation, only a few of them can give practicable enantioselectivities (> 90% ee). We report the synthesis of a new family of hybrid phosphine-phosphoramidite ligands. Their applications in Rh-catalyzed asymmetric hydroformylation afforded up to 99 % ee for styrene derivatives, 98 % ee for vinyl acetate derivatives and 96 % ee allyl cyanide, which represents the best result up to date. The relationship between the substituent and the enantioselectivity of the ligands was investigated by systematic variation on the ligand structure, which was successfully rationalized by Herrmann’s theoretical model with CAChe MM2 calculation.

The further application of phosphine-phosphoramidite ligands family in the rhodium-catalyzed asymmetric hydroformylation of a variety of allylic substrates achieved very high enantioselectivities (up to 99 % ee) and reactivities (up to 9700 turnover number) under mild conditions. To the best of our knowledge, this is the first
example of applying $N$-allylamides and $N$-allylsulfonamides in asymmetric hydroformylation, which provides an alternative catalytic route to $\beta^{2}$-amino aldehydes, acids, and alcohols for pharmaceutical and synthetic chemistry.

To increase the linear-selectivity in hydroformylation of olefins, especially the more accessible internal olefins, a new strategy for ligand design was developed by using tetraphosphorus ligands with multiple chelating modes to enhance chelating ability and regioselectivity. Based on this concept, two types of tetraphosphorus ligands, tetraphosphoramidite ligands and tetraphosphine ligands, were designed and synthesized. With tetraphosphoramidite ligand, the highest regioselectivity ever reported in the hydroformylation of both internal olefins and terminal olefins were achieved. Tetraphosphine ligands exhibited remarkably improved high temperature performance in the hydroformylation of terminal olefins.

Although $P$-stereogenic ligands have achieved excellent enantioselectivities in asymmetric hydrogenation, their development is still limited due to their synthetical difficulties. A new highly electron-donating, $P$-stereogenic bisphospholane ligand (named as ZhangPhos) was developed, which can be synthesized practically and highly enantioselectively from a commercially available chiral reagent. ZhangPhos exhibited extremely high enantioselectivities (up to 99 % ee) and reactivities (up to 50 000 TON) for rhodium-catalyzed hydrogenation of a wide range of functionalized olefin derivatives.
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ACKNOWLEDGEMENTS

First and foremost, I sincerely thank my research advisor, Dr. Xumu Zhang, not only for his precious guidance, encouragement, and support on the journey of pursuing my Ph.D. degree, but also for his inspiration and suggestions on my career development. My thankfulness also was extended to my former and current committee members: Dr. Thomas E. Mallouk, Dr. Harry R. Allcock, Dr. Gong Chen, Dr. Qing Wang, Dr. Marry Beth Williams, and Dr. Blake Peterson for their time and valuable discussions.

I want to acknowledge my research coworkers: Dr. Yongjun Yan, Dr. Shichao Yu, Dr. Guohua Hou, Dr. Baoming Ji, Mr. Bonan Cao and Mr. Kexuan Huang for their pleasant collaboration and helpful discussion. I am also very grateful to all the other past and present Zhang’s group members, Dr. Chunjiang Wang, Dr. Le Zhou, Dr. Duan Liu, Dr. Qin Yang, Dr. Qian Dai, Dr. Weicheng Zhang, Dr. Zhenlu Shen, Dr. Gao Shang, Dr. Xianfeng Sun, Dr. Weiran Yang, Ms. Yaping Zou, Mr. Wei Li, Ms. Tian Sun, Mr. Yuming, Chie, Mr. Stephen Spenalla, Ms. Huiling Geng, Mr. Guodu Liu. I had fun and pleasant memories in this harmonious family.

Finally and most importantly, I would like to express my deep gratitude to my wife, Xiangyue Wu for her wholehearted love and consideration, to my lovely daughter, Catherine for all the luck and happiness she brings to me, and to my parents. This entire dissertation belongs to all of my beloveds.
Chapter 1

An Introduction to Rhodium-Catalyzed Hydroformylation

1.1 Overview

Hydroformylation has been one of the most important homogenous catalysis processes that were largely applied in industry nowadays. It transforms olefins and syngas (CO/H₂) into aldehydes in one single, atom economic step.¹

![Hydroformylation Reaction Scheme](image)

Scheme 1-1: Hydroformylation Reaction

The Hydroformylation of alkenes was first discovered by Otto Roelen in 1938.² This seminal work was based on cobalt carbonyl catalyst with harsh conditions and low reactivity. The first rhodium-catalyzed hydroformylation was reported by Wilkinson group in the middle of 1960’s. It was found that rhodium complexes modified by phosphine ligands can make hydroformylation run at mild conditions with much higher activity and selectivity comparing to cobalt catalysts.³ The detailed studies on phosphine ligands revealed that the variations on phosphine ligands can significantly affect the
reaction rate and selectivity. Thus, modern research on hydroformylation focuses mainly on phosphorus ligands modified rhodium catalysts and its applications.\(^4\)

Hydroformylation has been widely applied in the synthesis of intermediates both for industries and research laboratories, due to the versatile functionality of the aldehydes obtained through the hydroformylation reaction. It is convenient to further convert aldehyde products into alcohols, amines, carboxylic acid derivatives, and other high valued chemicals. Linear aldehydes are important raw materials for fine chemicals, in particular for detergents and polymer plasticizer. Optically active aldehydes, produced by the asymmetric version of hydroformylation, are versatile intermediates for the synthesis of many biologically active compounds, pharmaceuticals and natural products.\(^1\)\(^g\)

Due to the favorable effects of phosphorus ligands in rhodium-catalyzed hydroformylation, this section primarily reviews the development of phosphorus ligands for both of linear-selective hydroformylation and asymmetric hydroformylation.

**0.2 Mechanism for Rhodium-Catalyzed Hydroformylation**

Extensive mechanistic studies have been reported among which the so-called dissociative mechanism proposed by Breslow and Heck is widely accepted as the catalytic cycle of hydroformylation (Scheme 0-2).\(^1\)\(^6\)\(^5\) Although it was first proposed for cobalt-catalyzed hydroformylation, this mechanism is applicable for rhodium complex-catalyzed hydroformylation with chelating monophosphines and diphosphines.

In this mechanism, the trigonal bipyramidal complex 1 (18-electron species) is believed to be a key active catalyst species which is formed by the reaction rhodium
precursor with ligands (L) in the presence of CO and H₂. The dissociation of one carbon monoxide from this complex generates a 16-electron coordinatively unsaturated species 2. The main catalytic cycle starts from the coordination of olefin to the rhodium center in the equatorial position, forming a trigonal bipyramidal hydrido olefin complex 3/3'. The subsequent olefin insertion into the Rh-H bond generates tetragonal alkyl rhodium complexes 4 and 5 (leading to linear and branched products, respectively), which was revealed to be the key step determining the regio- and enantioselectivity of the hydroformylation reaction. Next, the coordination of carbon monoxide to the rhodium center generates trigonal bipyramidal complexes 6 and 7, respectively, which is followed by migratory insertion of the alkyl group to one of the coordinated carbon monoxide yields tetragonal acyl complexes 8 and 9. Oxidative addition of molecular hydrogen affords tetragonal bipyramidal rhodium complexes 10 and 11. Finally, Reductive elimination yields the linear aldehyde 12 and the branched aldehyde 13, and regenerates the catalytically active species 2.
Scheme 0-2: Mechanism for Rhodium-Catalyzed Hydroformylation.
0.3 Phosphorus Ligands for Rhodium-Catalyzed Linear-Selective Hydroformylation

Due to the high demand of normal aldehydes in chemical industry, especially for the preparation of polymer plasticizers and detergents, hydroformylation of terminal olefins has become one of the largest applications of homogeneous catalysis in industry. For example, the hydroformylation of propylene is employed in the large-scale preparation of the normal butanal (Scheme 1-3). Butanal and the reductive product, butanol are important solvents and raw materials for ester and detergents industry. More importantly, most of its production is transformed into 2-ethylhexanol (2-EH) through consecutive aldol condensation and reduction. 2-EH reacts with phthalic anhydride to give bis(2-ethylhexyl) phthalate (DEHP), which is an important plasticizer to make PVC flexible with approximately annual output of three billion kilograms.¹

Scheme 0-3: Hydroformylation of Propylene and The Application Thereof.
Since internal olefins are cheaper and more readily available feedstock than terminal olefins, the direct hydroformylation of internal olefins to produce linear aldehydes is of great importance from the economic and energy points of view. This is so-called isomerization-hydroformylation (Scheme 0-4).

Scheme 0-4: Isomerization-Hydroformylation of Internal olefins.

Most of the current hydroformylation processes in industry are based on rhodium-monophosphines catalyst. Especially in the early stage of hydroformylation, monophosphorus ligands predominated both in academia and industry. Recently, bidentate phosphorus ligands have attracted much more attention because they generally afford higher regioselectivities and reactivities. The representative ligands for each of the categories will be demonstrated here.

### 0.3.1 Monophosphorus Ligands for Linear-Selective Hydroformylation

Other than triphenylphoshine, the earliest and most common monophosphorus ligand in hydroformylation, tris-\textit{m}-sulfonatophenylphosphine (tppts), 14, is one of the important ligands in the history of hydroformylation. It was used in the Ruhrchemie/Rhône-Poulenc hydroformylation process by Celanese. Pruett and Smith of Union Carbide Corporation reported the use of bulky monophosphorus ligands 15, in
rhodium-catalyzed hydroformylation, which introduced another important type of ligands, phosphite ligands (Figure 1-1).8

More recently, Breit and coworkers reported a phosphabenzene ligand 16, which exhibits very high reactivity in rhodium-catalyzed hydroformylation.9 Breit and coworkers also developed an interesting phosphabarrelene ligand 17 (Figure 1-1). The rhodium complex of ligand 17 catalyzed hydroformylation of internal olefin without isomerization reactions.10

Figure 1-1: Monophosphorus Ligands for Linear-Selective Hydroformylation.
0.3.2 Bisphosphorus Ligands for Linear-Selective Hydroformylation

*Diphosphine Ligands:*

Diphosphine ligand, Bisbi 18 (Figure 1-2), represents a breakthrough in the ligand development for hydroformylation, which is the first example of diphosphine ligand in this area. Bisbi 18 was developed by Devon and coworkers at Eastman Kodak in 1987 and provided exceptionally high regioselectivity for the hydroformylation of propene.\(^{11}\) Since then, a number of diphosphine ligands were employed in linear-selective hydroformylation of alkenes, such as dppe 19, 2,5-dppm-nor 20, and T-BDCP 21 (Figure 1-2).\(^{18}\) However, most of them gave low regioselectivities, which could be explained by the concept of the natural bite angles. Casey and Whitaker systematically investigated the correlation between ligand bite angles and the regioselectivity in hydroformylation. It was found that ligands with a P-Rh-P angle of near to 120 °, upon coordinating to rhodium center, can afford high regioselectivity in hydroformylation.\(^{12}\)

Based on this ‘natural bite angle’ concept, a family of diphosphine ligands, XantPhos (Figure 1-2) was developed by van Leeuwen and coworkers and proved to be one of the best ligands for linear-selective hydroformylation. For example, Xantphos 22 achieved linear/branched ratios of up to 53:1 in the hydroformylation of 1-octene.\(^{10}\) Some other Xantphos analogous that cover a range of bite angles from 102 to 121° also showed high activity and regioselectivity in the rhodium-catalyzed hydroformylation of both terminal and internal octenes, which includes dibenzophosphophonyl and phenoxaphosphanylsubstituted XantPhos type ligands 23 and 24,\(^{13}\) Homoxantphos 25, Sixantphos 26, Thixantphos 27, and Nixantphos 28 (Figure 1-2).\(^{14}\)
Beller and coworkers reported that NaPhos ligands 29 with strong electron-withdrawing substituents gave very high linear/branched ratio ($n:i$ of up to 9.5:1) in the hydroformylation of internal olefins to linear (Figure 1-2). $^{15}$

Figure 1-2: Diphosphine Ligands for Linear-Selective Hydroformylation.
**Diphosphite Ligands:**

Diphosphite ligands represent another important family of ligands for highly linear-selective hydroformylation and have attracted a large research effort at academia and industries (Figure 1-3). Right after the initial reports on Biphephos 30 by Bryant and coworkers at Union Carbide, diphosphites were recognized as a new generation of ligands in rhodium-catalyzed hydroformylation. Bulky diphosphite ligands showed much higher selectivity than monophosphite. A variety of functionalized olefins were hydroformylated with Rh-Biphephos catalyst under mild reaction conditions, and linear/branched ratios of over 40:1 were achieved, with a high tolerance to functional groups, such as carboxylic acids and halides. The selectivity of bulky diphosphite ligands was found to be very sensitive to the bridge length and bisphenol was proved to be the most successful linkage. van Leeuwen and coworkers also reported unsymmetrical Biphephos derivative 31 which showed high regioselectivity in the hydroformylation of terminal olefins with linear/branched ratios of up to 48.

Diphosphite ligand 32, based on binol backbone, was reported by Du Pont and DSM. The selectivity to linear aldehyde was reported up to 97 % for the hydroformylation of 2-hexene.

Paciello and coworkers designed and synthesized a chelating diphosphite ligand 33 based on well-defined supramolecular backbone, p-tert-butyl calix[4]arene. Ligand 33 achieved very high regioselectivity in the rhodium-catalyzed hydroformylation of 1-octene.
Another class of interesting bulky diphosphites, unsymmetrical phosphite-acylphosphite ligands was reported by Börner and coworkers for the hydroformylation of \( n \)-octene mixtures with very high activities and linear-selectivities (Figure 1-3).\(^{21}\)

![Figure 1-3: Bulky Diphosphite Ligands for Linear-Selective Hydroformylation](image-url)
**Diphosphoramidite Ligands:**

Another important family of ligands for highly linear-selective hydroformylation is the diphosphoramidite ligands (Figure 1-4). A bidentate pyrrole-based phosphoramidite ligand 35 was employed by van Leeuwen in the hydroformylation of 1-octene and very high selectivity to linear aldehyde (linear/branched ratio up to 100) has been achieved. A fast isomerization rate for internal olefins was also observed and was attributed to its high electron-withdrawing property rather than bite angle and steric hindrance.

Other diphosphoramidite ligands include electron-withdrawing N-sulfonylphosphoramidite ligand 36, developed by Hersh and coworkers, and Xantphos derivative 37. However, both of them only obtained moderate linear-selectivity in rhodium-catalyzed hydroformylation of alkenes.

![Figure 1-4: Diphosphoramidite Ligands for Linear-Selective Hydroformylation.](image)

![Figure 1-4: Diphosphoramidite Ligands for Linear-Selective Hydroformylation.](image)
0.3.3 Miscellaneous Ligands for Linear-selective Hydroformylation

Complementary to design and synthesis of phosphorus ligands for linear-selective hydroformylation, a number of new strategies were developed to increase the selectivity and practicability of this process.

Based on a concept of self-assembly of monodentate to bidentate ligands, Breit developed a new type of ligand 38 through the hydrogen bonding of 6-(diphenylphosphino) pyridin-2(1H)-one with its hydroxypyridine tautomer. Ligand 38 was robust under the hydroformylation condition and achieved high regioselectivity in the hydroformylation of a wide range of functionalized terminal olefins. van Leeuwen and coworkers reported another type of wide-bite-angle diphosphines by assembly of ditopic ligands for rhodium-catalyzed hydroformylation, for example ligand 39 (Figure 1-5). The assemblies gave high selectivities for linear product in the hydroformylation of 1-octene.

Another strategy that usually used to enhance the selectivity of a reaction is substrate bound catalyst-directing groups. Breit research group reported that Ph₂POMe was a suitable catalytic directing group for hydroformylation of homoallylic alcohols. Tan and coworkers designed and synthesized an alkoxy benzoazaphosphole scaffolding ligand 40, which obtained very high selectivity in the rhodium-catalyzed hydroformylation of allylic alcohols and allylic sulfonamides to the construction of quaternary carbon centers (Figure 1-5).
0.4 Chiral Phosphorus Ligands for Rhodium-Catalyzed Asymmetric Hydroformylation

Asymmetric hydroformylation is of great importance for the pharmaceutical and fine chemical industries because it produces chiral aldehydes from inexpensive feedstock (alkenes and syngas) in a single atom-economic step. Enantiomerically pure aldehydes are valuable intermediates for synthesizing a variety of biologically active compounds and natural products. For example, asymmetric hydroformylation of vinylarenes followed by oxidation can affords enantiomerically pure 2-arylpropanoic acids such as Ibuprofen, Ketoprofen and Naproxen, which are important nonsteroidal anti-inflammatory agents.

Although its promising application in organic synthesis, the development of asymmetric hydroformylation is later than the linear-selective type. In a long period, the reported enantioselectivities in asymmetric hydroformylation were less than 60 % ee. Until 1992, an important breakthrough was made by Babin and Whiteker at Union Carbide. Since then, considerable progress has been achieved in the development of
chiral phosphorus ligands for rhodium-catalyzed asymmetric hydroformylation, which will be briefly reviewed in this section.

0.4.1 Bisphosphorus Ligands for Asymmetric Hydroformylation

*Diphosphite Ligands:*

In 1992, Babin and Whiteker reported the first successful ligand for highly enantioselective hydroformylation, Chiraphite 41 (Figure 1-6).\(^\text{30}\) Chiraphite 41 is a bulky diphosphite ligand with a chiral \((2R, 4R)\)-pentane-2, 4-diol backbone, which achieved excellent enantioselectivities (up to 90 % ee) in the asymmetric hydroformylation of styrene under mild reaction conditions. The steric hindered substituents, \(\tau\)-butyl groups were believed to transfer the chiral information of the backbone to the non-chiral biphenyl moieties. The less electron-donating property of diphosphite ligands enables hydroformylation to be conducted at relatively low temperature which is preferable to high enantioselectivity. Thus, chiral diphosphite ligands have become a major family of ligands in asymmetric hydroformylation.

Encouraged by the success of Chiraphite 41, a lot of research groups developed more chiral diphosphite ligands by changing chiral backbone, as well as introducing chiral element into the phosphite moiety. With chiral spiro [4.4]nonane-1,6-diol backbone, Chan and coworkers developed chiral diphosphite ligands 42 and 43.\(^\text{31}\) Their employment in the asymmetric hydroformylation of styrene gave moderate enantioselectivities (up to 65% ee).
Chiral sugar scaffold also was introduced into asymmetric hydroformylation as backbone for chiral diphosphite ligands. The first diphosphite ligand based on sugar, ligand 44, was reported by Van Leeuwen and coworkers and afforded moderate enantioselectivities (65 % ee) in the hydroformylation of styrene derivatives.32 Diéguez group developed a series of diphosphite ligand 45 bearing a furanoside backbone, which achieved excellent enantioselectivities (up to 91%) in the hydroformylation of styrene derivatives.33

Some other optically active diols were utilized as building blocks for the synthesis of chiral diphosphite ligands. Freixa and coworkers reported diphosphite ligand 46 with a chiral macrocyclic backbone which gave moderate enantioselectivity (up to 76 % ee) in the asymmetric hydroformylation of styrene.34 Zhang group developed a family of diphosphite ligands 47 based on chiral BINOL backbone.35 Moderate enantioselectivities (up to 80% ee) and excellent regioselectivities (b/l up to 98/2) have been achieved in the Rh-catalyzed asymmetric hydroformylation of vinyl acetate.

Chiral backbone is not necessary to achieved high enantioselectivity for diphosphite ligands. Klosin and coworkers at Dow Chemical reported a ligand, Kelliphite 48, bearing a non-chiral 2,2'-biphenol backbone and chiral phosphite moieties.36 With Kelliphite 48, good enantioselectivity (80 % ee) and activity were obtained in the asymmetric hydroformylation of allyl cyanide.
Figure 1-6: Chiral Diphosphite Ligands for Asymmetric Hydroformylation.
**Phosphine-phosphite Ligands:**

Binaphos 49, developed by Takaya and Nozaki in 1993, represents another breakthrough in rhodium-catalyzed asymmetric hydroformylation (Figure 1-7). This hybrid phosphine-phosphite ligand based on binaphthyl backbone is recognized as the first efficient chiral ligand that has a broad substrate adaptability. The ligand has been investigated in the asymmetric hydroformylation of a variety of prochiral olefins and proved to be efficient for styrene derivatives and vinyl carboxylates. For example, up to 94 % ee and 92 % ee has been achieved in the asymmetric hydroformylation of styrene derivatives and vinyl carboxylates, respectively.

Encouraged by the excellent enantioselectivity, modifications of the structure of Binaphos 49 have been studied. It was found that changing the phenyl groups into substituted aryl groups and/or introducing substituent group onto the 3,3'-position of binaphthyl group of Binaphos 49 resulted in slightly improved enantioselectivity.37c, 38 Biphemphos 50, a Binaphos analogue bearing a chiral biphenyl backbone, also afforded very high enantioselectivity that is comparable to Binaphos 49.37b,39

Binophos 49 was stabilized on to polymer resin for the recovery and reuse of the catalyst. Highly cross-linked polymer-supported Binophos ligands 51 were effective for the hydroformylation of styrene (up to 89% ee).40

Based on P-chiral phosphine moiety, van Leeuwen and coworkers reported phosphine-phosphite ligand 52, which achieved enantioselectivity of 63 % ee in the asymmetric hydroformylation of styrene.41
Figure 1-7: Phosphine-phosphite Ligands for Asymmetric Hydroformylation.

*Phosphine-phosphoramidite Ligands:*

Based on 1,2-dihydroquinoline backbone, Leitner reported a new phosphine-phosphoramidite ligand, QUINAPhos 53 (Figure 1-8), which obtained good enantioselectivity (up to 74 % ee) in the asymmetric hydroformylation of styrene.42

Reek group reported two family of phosphine-phosphoramidite ligands, IndolPhos ligands 54 and 55,43 derivated from Binol and Taddol, respectively. IndolPhos ligands afforded moderate to good enantioselectivities (up to 74 % ee) in the asymmetric hydroformylation of styrene, vinyl acetate, and allyl cyanide.
Bisphosphacyclic Ligands:

Another class of successful phosphorus ligands for rhodium-catalyzed hydroformylation is bisphosphacyclic ligands, as showed in Figure 1-9.

C$_2$-Symmetric bisphospholane-type ligands, ($S$,$S$)-Esphos 56 developed by Wills et al., provide high enantioselectivity (up to 90 % ee) for asymmetric hydroformylation of vinyl acetate but are unselective for styrene.\(^{44}\)

Landis and coworkers developed a new family of bis-3,4-diazaphospholane ligands 57 and achieved good to excellent enantioselectivities in the rhodium-catalyzed asymmetric hydroformylation of three standard substrates (up to 82 % ee, 96 % ee and 87 % ee for styrene, vinyl acetate and allyl cyanide, respectively).\(^{45}\)

Inspired by the excellent enantioselectivities of bis-3,4-diazaphospholanes 57, Klosin and coworkers investigated a variety of bisphosphacyclic ligands in asymmetric hydroformylation. ($R$, $R$)-Ph-BPE 58 was found to be an excellent ligand for asymmetric hydroformylation and up to 94 % ee, 82 % and 90 % ee were obtained in the hydroformylation of styrene, vinyl acetate and allyl cyanide, respectively.\(^{46}\) They also found that several P-chiral bisphospholane ligands, originally developed for asymmetric

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Figure 1-8: Phosphine-phosphoramidite Ligands for Asymmetric Hydroformylation.
hydrogenation by Zhang group, provided very high enantioselectivities in asymmetric hydroformylation. For the three standard substrate, (S,S,R,R)-TangPhos 59 achieved up to 90 % ee, 93 % ee and 83 % ee, respectively, while (S,R)-BINAPINE 60 obtained up to 94 % ee, 94 % ee and 87 % ee, respectively. Recently, a class of C₂-symmetric bidentate phosphonite ligands 61, reported by Ding’s group, also displayed high selectivity (up to 79 % ee, 91 % ee and 79 % ee for standard substrates, respectively) in rhodium-catalyzed asymmetric hydroformylation. 48

Figure 1-9: Bisphosphacyclic Ligands for Asymmetric Hydroformylation.
0.4.2 Monophosphorus Ligands for Asymmetric Hydroformylation

Despite the successful use of monodentate ligands in many transition-metal catalysed reactions, their use in asymmetric hydroformylation only provide moderate enantioselectivities. For example, monophosphite ligand 62 gave 38 % ee, 8 % ee and 43 % ee for the three standard substrates. One of the few high enantioselectivities of monophosphorus ligands was reported by Ojima and coworkers. Monophosphoramidite ligand 63 obtained good enantioselectivity (80 % ee) in the asymmetric hydroformylation of allyl cyanide.

![Chemical structures](image)

Figure 1-10: Monophosphorus Ligands for Asymmetric Hydroformylation.

0.5 Objectives

Rhodium-catalyzed linear-selective hydroformylation has being widely employed in industry for massive production of linear aldehydes, which are very important raw materials for polymer and detergent industries. From the economic point of view, it is still highly desirable to develop new phosphorus ligands to further enhance the linear-selectivity. Especially for isomerization-hydroformylation of internal olefins, the
regioselectivity achieved with current ligands is far from satisfactory. Another challenge that is important to industry is the hydroformylation of longchained olefins; in these cases, the produced aldehydes have high boiling points and thus require high-temperature distillation during the production process, which means that the ligands used in the reaction must be tolerant towards high temperatures.

Asymmetric hydroformylation is a very promising catalytic reaction that converts olefins into enantiomerically pure aldehydes in an atom economic manner. Although asymmetric hydroformylation offers great potential application for organic synthesis, it is still seldom utilized by industry mainly because of several well-known challenging issues. First, high enantioselectivities are usually obtained from the hydroformylation reactions carried out at low temperature, accompanying with relatively low reaction rate and conversion. Second, it is difficult to achieve good reactivity, regio- and enantioselectivities under the same condition. Finally, racemization of the aldehyde products, particularly those from styrene derivatives, is observed under hydroformylation reaction conditions. During the past decades, numerous chiral ligands have been developed for asymmetric hydroformylation, however, few of them can afford enantioselectivities of over 90% ee.

To address the above challenges in rhodium-catalyzed hydroformylation, the objectives of this graduate research have been focused on developing new phosphorus ligands for this methodology. In practice, efforts towards this goals have been devoted into three aspects: a) design and synthesis of new phosphorus ligands; b) Testing the new ligands in the hydroformylation of standard substrates and investigating the relationship of ligand structure and selectivity; c) exploring more challenging substrates and further
application of new catalytic system. The detailed results will be presented in the following chapters.
References


Chapter 2

Synthesis and Application of Modular Phosphine-phosphoramidite Ligands in
Asymmetric Hydroformylation: Structure-Selectivity Relationship

2.1 Introduction

Hydroformylation is one of the most important reactions that still widely
employed in industry, which provides aldehydes directly from alkenes and syngas
(CO/H₂) in one single step (Scheme 2-1). Millions of tons of oxo products produced
worldwide per year make it regarded as the largest industrially homogeneous catalytic
process.¹

Scheme 2-1: Hydroformylation Reaction.

In particularly, asymmetric hydroformylation (AHF) has attracted much attention
as an atom economic method to convert olefins into enantiomerically pure aldehydes.
Aldehyde is not only widely present compound in nature, but also a versatile
functionality which can be easily transformed into corresponding alcohol, acid and
amine. Therefore, chiral aldehydes are also used as precursors for synthesizing a variety
of biologically active products and fine chemicals.\textsuperscript{1-3} Although AHF offers promising application for organic synthesis, it is still seldom utilized by industry mainly because of several well-known challenging issues. First, high enantioselectivities are usually obtained from the hydroformylation reactions carried out at low temperature, accompanying with relatively low reaction rate and conversion. Second, it is difficult to achieve good reactivity, regio- and enantioselectivities under the same condition. Finally, racemization of the aldehyde products, particularly those from styrene derivatives, is observed under hydroformylation reaction conditions.\textsuperscript{1b}

Although new ligands that are able to provide chiral aldehydes at considerable high temperatures without sacrificing their selectivities are highly desirable, only a few successful examples were documented in the past two decades (Scheme 2-2). Bidentate phosphite ligands were proved to be active in AHF reactions, such as (2\textit{R}, 4\textit{R})-chiraphite (1)\textsuperscript{4} and (\textit{S}, \textit{S})-kelliphite (2).\textsuperscript{5} The former ligand shows high enantioselectivity (nearly 90\% ee) for the hydroformylation of styrene and the later one is effective for allyl cyanide [75\% ee, b/l (branched/linear ratio) = 16] and vinyl acetate (88 \% ee, b/l = 56) at low temperature. Another class of successful ligands is $C_2$-symmetric bisphospholane. (\textit{S}, \textit{S})-esphos (3),\textsuperscript{6} reported by Wills, provides a high selectivity for vinyl acetate (90 \% ee, b/l = 16), but nearly no enantioselectivity for styrene. Landis, Klosin and co-workers reported the diazaphospholane ligand 4 and its analogues,\textsuperscript{7} which were applied in the AHF of styrene, vinyl acetate and allyl cyanide with high enantioselectivities (82, 96, 87 \% ee, respectively) and regioselectivities (b/l = 7, 4, 37, respectively) even at elevated temperature. Recently, a class of $C_2$-symmetric bidentate phosphonite ligands, reported by Ding’s group, also displayed high selectivity in Rh-catalyzed AHF of the above
olefins. Among all the ligands reported hitherto, hybrid ligands bearing different phosphorus structure have been regarded as the best in AHF. The major breakthrough in this area was made in 1993, when Takaya and Nozaki reported \((R,S)\)-binaphos (6) which offered generally high enantioselectivities in the AHF of a variety of prochiral olefins (up to 94 % ee, \(b/l = 7.3\) for styrene). However, with binaphos as the ligand, chiral aldehyde products underwent racemization under the condition of rhodium-catalyzed hydroformylation, especially with a long reaction time. It is still highly desirable to develop new ligands for highly enantioselective hydroformylation without racemization.
In this chapter, we report the synthesis of a new family of hybrid phosphine-phosphoramidite ligands 7 (as shown in Figure 2-1) as well as their applications in Rh-catalyzed AHF of styrene, vinyl acetate, allyl cyanide and their derivatives with good to excellent regio- and enantioselectivities (up to 99 % ee). The modular character allows systematic variation on the ligand structure, which was utilized to investigate the relationship between the ligand structure and their control of enantioselectivity. We
envision that understanding of the structure-selectivity relationship can provide useful
guidance for ligand design and experimental data for optimizing the current theoretical
models in asymmetric hydroformylation.

2.2 Results and Discussion

2.2.1 Design and Synthesis of Phosphine-Phosphoramidite Ligands

Despite the structural similarity, there are significant differences between
binaphos and our new phosphine-phosphoramidite ligands. Comparing to binaphos, the
phosphine-phosphoramidite ligands are more electron-donating since the
electronegativity of nitrogen (3.04) is less than that of oxygen (3.44). Sterically, the \( N \)-substituent on phosphoramidite group can make the active catalytic complex show a
deeper and more closed chiral pocket than that of binaphos, based on the models from
CAChe MM2 calculation.\(^\text{11}\) Takaya and co-workers have concluded that configuration
matched (\( R,S \) and \( S,R \))-binaphos showed better selectivity than the mismatched (\( R,R \) and
\( S,S \))-binaphos. As analogues of binaphos, the new hybrid phosphine-phosphoramidite
ligands were synthesized with two enantiomerically opposite binaphthyl groups.

Firstly, we synthesized ligands 7a, 7b (named as YanPhos)\(^\text{10}\) and 7c with methyl,
ethyl and benzyl group, respectively, attached to nitrogen atoms to investigate the
influence of the \( N \)-substituents (Scheme 2-2). Starting from (\( \delta \))-BINOL (1,1'\text{-bi-2-
naphthol}) 8, ditriflate 9 was obtained in 95 % yield by reaction with triflic anhydride
under basic conditions. Following the slightly modified Hayashi’ procedure,\(^\text{12}\) the
monophosphonylation of 9 was carried out with diphenylphosphine oxide, catalytic amount of palladium diacetate and 1,4-bis(diphenylphosphino)butane (dppb) in dimethyl sulfoxide at 120 °C, which gave 95 % yield of (S)-10 without racemization. The reaction of (S)-10 with potassium cyanide in the presence of nickel bromide as a catalyst and activated zinc powder afforded quantitatively (S)-11, which was oxidized into amide (S)-12 with hydrogen peroxide according to the procedures reported by Sumi et al.13 (S)-12 underwent a Hofmann rearrangement with bromine in a basic methanol solution to give carbamate (S)-13 in 83 % yield. (S)-13 was directly reduced by borane to afford phosphine-amine (S)-14a with N-methyl group. On the other hand, alkaline hydrolysis of (S)-13, followed by acylation with acetyl chloride or benzoyl chloride and then borane reduction, afforded phosphine-amine (S)-14b and (S)-14c with N-ethyl and N-benzyl substituents, respectively. After deprotonation with n-BuLi and quenching the derived anion with phosphorochloridite, the desired ligand (S, R)-7a-c were obtained in 33-42 % yields as air-stable solid.
Scheme 2-2: Synthesis of Phosphine-phosphoramidite Ligands \((S,R)-7a-c\).
To disclose the steric effect of the phosphoramidite moiety, the binaphthyl group of the phosphoramidite part was introduced methyl groups on the 3,3'-position (ligand 7d) or switched into sterically more bulkyl di-\(\tau\)-butyl substituted biphenyl group (ligand 7e and 7f, Scheme 2-3), fixing the \(N\)-substituent as ethyl group. Those bulkyl substituents spatially adjacent to P atom were expected to make the chiral pocket more closed and further define the asymmetric environment around the catalytic center.

In the course of synthesizing ligands 7, a more concise synthetic route for intermediate 14 was discovered attributing to the availability of \((R)\)-NOBIN (2-amino-2'-hydroxy-1,1'-binaphthyl) 16. Following the literature procedure,\(^\text{14}\) the acetylation of chiral \((R)\)-NOBIN 16 with acetic anhydride provided the hydroxyl amide 17, which was transformed into the \(N\)-protected triflate 18 in 91 % yield. Palladium catalyzed phosphinoylation of the triflate 18 afforded the phosphine oxide amide 19 in 84 % yield. Phosphine-amine 14 was obtained in 49 % yield by simultaneous reduction of phosphine oxide and amide groups with excess BH\(_3\)·(CH\(_3\))\(_2\)S, followed by treatment with diethylamine. After deprotonation with \(n\)-BuLi and quenching the derived anion with phosphoroehalogenidite 15a, 15d-f, the desired ligand \((R, S)\)-7b and 7d-e were obtained in 37-52 % yield as off-white air-stable solid.
Scheme 2-3: Synthesis of phosphine-phosphoramidite ligands (R,S)-7b, 7d-f.
2.2.2 Application of Ligand 7 in Asymmetric Hydroformylation

Before applying these novel phosphine-phosphoramidite ligands in Rh-catalyzed asymmetric hydroformylation, the optimized reaction condition was obtained by using \((R,S)-7b\) as representative ligand and styrene (20) as standard substrate. The AHF reactions were carried out with 0.1 mol % of catalyst loading and 1:1 CO/H\(_2\) gas. The catalyst was prepared \textit{in situ} by mixing Rh(acac)(CO)\(_2\) with ligand \((R,S)-7b\) at certain ratios.

The ligand/Rh ratio significantly influenced the hydroformylation reaction. As shown in Table 2-1, entries 1-4, increasing the ligand/Rh ratio from 1:1 to 4:1 improved both regioselectivity (b/l from 3.0 to 7.3) and enantioselectivity (from 21 to 98 % ee), but further increasing the ratio to 6:1 did not result in improvement.

Screening the reaction solvent showed that nonpolar solvents, such as benzene and toluene, offered high enantioselectivities (Table 2-1, entries 3, 5-8). Increasing reaction temperature led to higher conversion but lower ee values (Table 2-1, entries 1, 9 and 10). As high as 99 % ee was obtained when the reaction was run at 40 °C with 25 % conversion, while the ee value dropped to 81 % at 80 °C. The best temperature for this catalyst system is 60 °C where full conversion and 98 % ee were achieved.

The syngas pressure did not influence the enantioselectivity but impacted the reactivity dramatically (Table 2-1, entries 3, 11 and 12). The higher CO/H\(_2\) pressure resulted in lower conversion which is mainly because the equilibrium of CO coordination to Rh centre is shifted more towards carbonyl bound Rh species at high pressure. The longer reaction time only slightly decreased the enantioselectivity (Table 2-1, entries 3,
13 and 14). The racemization of the Rh/7b catalyzed AHF was markedly lower than that of binaphos. All of the above hydroformylation reactions provided high chemoselectivities (no hydrogenation product was detected according to $^1$H NMR analysis) and good regioselectivities, while the enantioselectivities strongly depended on reaction conditions. Entry 3 in Table 2-1 represents the optimized reaction condition for phosphine-phosphoramidite ligands.
Table 2-1: Optimization of Rh-Catalyzed Asymmetric Hydroformylation of Styrene with (R,S)-7b

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<th>Entry</th>
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<th>Solvent</th>
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<th>time[h]</th>
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</table>

a All reactions were carried out with substrate/Rh =1000. b Conversions and branched-linear ratio (b/l) were determined on the basis of 1H NMR. c Determined by converting the
aldehyde to the corresponding alcohol with NaBH₄ followed by GC analysis (Supelco's Beta Dex 225). The absolute configuration \((R)\) was assigned by comparing the sign of the optical rotation of the resulting alcohol with \((R)-2\)-Phenylpropan-1-ol.

With the optimized reaction condition, we systematically investigated the structure-selectivity relationship of phosphine-phosphoramidite ligands. Three most commonly used standard substrates: styrene \((20)\), vinyl acetate \((23)\) and allyl cyanide \((26)\) were utilized to examine the regio- and enantioselectivities of this series of ligands 7a to 7f in Rh-catalyzed AHF (Table 2-2).

The impact of the \(N\)-substituent to the ligand selectivity was examined by comparing the performance of ligand 7a, 7b and 7c (Table 2-2, entries 1-3). Increasing the steric bulk of \(N\)-substituent from methyl to benzyl group slightly elevated the regioselectivity and decreased the enantioselectivity. \(N\)-Ethyl substituted ligand, \((S,R)\)-7b, provided hitherto the best enantioselectivities for Rh-catalyzed AHF with 98 % ee for styrene and 96 % ee for vinyl acetate (Table 2-2, entries 2). It is worthwhile to note that, with \((S,R)\)-7b as ligand, the hydroformylation of allyl cyanide afforded as high as 96 % ee, which is higher than the previously best enantioselectivity (94 % ee at 49 % conversion) achieved by Binapine,\(^{15}\) a ligand developed in our group for hydrogenation. \(N\)-Methyl substituted ligand, \((S,R)\)-7a gave slightly lower regio- and enantioselectivities to the three substrate than that of \((S,R)\)-7b (Table 2-2, entries 1). Similarly, \(N\)-benzyl substituted ligand, \((S,R)\)-7c also gave slightly lower regio- and enantioselectivities than that of \((S,R)\)-7b, although slightly higher regioselectivities were obtained for vinly acetate.
and allyl cyanide (Table 2-2, entries 3). Overall, the variation of $N$-substituent does not exert obvious influence on the selectivities of phosphine-phosphoramidite ligands.

As a counter enantiomer, ($R$,$S$)-7b showed almost equal regio- and enantioselectivities for all the three substrates as ligand ($S$,$R$)-7b did, except for the contrary absolute configuration of the products (Table 2-2, entries 2 and 4). Fixing on the $N$-ethyl group on the phosphine-amine moiety, we investigated the steric effect of phosphite part to the regio- and enantioselectivities of phosphine-phosphoramidite ligands. ($R$,$S$)-7d, with two methyl groups on the 3,3'-position of binaphthyl part, did not display higher enantioselectivity than corresponding ($R$,$S$)-7b as expected (Table 2-2, entries 4 and 5). Unlike the case of binaphos where the two more methyl groups led much higher reactivity and enantioselectivity,9c ($R$,$S$)-7d resulted in decreased reactivity and ee values, albeit with higher regioselectivities for styrene and vinyl acetate (b/l = 8.0 and 65.2 respectively). Although possessing a even more steric bulky phosphoramidite fragment than ($R$,$S$)-7d, ($R$,$S$)-7e was proved to be less effective in asymmetric induction with only moderate ee values for the three substrates (66, 65, and 65 %, respectively, Table 2-2, entry 6). The improvement was the higher regioselectivity for styrene (b/l = 27.6). To investigate the role of the chirality of phosphoramidite unit, ($R$)-7f was prepared and used in AHF. In contrast to ($R$,$S$)-7e, the loss of one chiral center did not result in negative effect on the enantioselectivity, but slightly higher ee values (75, 66 and 69 % respectively, Table 2-2, entry 7). It is worthwhile to note that ($R$)-9f afforded as high regioselectivity as b/l = 56.6, which is the best result in this condition to our best knowledge. The overall trend is that increasing the steric bulkiness of phosphoramidite
moiety will diminish the enantioselectivity, but will benefit the regioselectivity for the
AHF of styrene.

In order to investigate the effect of ligand structure to their catalytic activities, we
applied ligands 7a-f in the AHF of styrene with 3 h reaction time (as shown in
parentheses in Table 2-2). It was found that the N-substituents did not influence the ligand
activity very much. The conversions of styrene with ligand 7a-c were 24, 22 and 22
percent, respectively. The activity of 7d was much slower than other ligands, which is
possibly due to its poor solubility in toluene. Ligand 7e and 7f resulted in higher activity
with 27 % and 29 % conversion, respectively.
Table 2-2: Rh-catalyzed AHF of Styrene, Vinyl Acetate and Allyl Cyanide with Phosphine-phosphoramidite Ligands.\(^a\)

\[
\begin{align*}
\text{R} & + \text{CO/H}_2 & \xrightarrow{\text{Rh(acac)}(\text{CO})_2/L} & \text{R}^*\text{CHO} + \text{R} - \text{CHO} \\
20: \text{R} = \text{Ph} & & 21: \text{R} = \text{Ph} \\
23: \text{R} = \text{AcO} & & 24: \text{R} = \text{AcO} \\
26: \text{R} = \text{CNCH}_2 & & 27: \text{R} = \text{CNCH}_2 \\
\end{align*}
\]

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<td>95(R)</td>
<td>99</td>
<td>4.1</td>
<td>93(S)</td>
</tr>
<tr>
<td>4</td>
<td>(R,S)-9b</td>
<td>99(22)(^d)</td>
<td>7.2</td>
<td>98(R)</td>
<td>76</td>
<td>13.5</td>
<td>96(S)</td>
<td>99</td>
<td>4.0</td>
<td>96(R)</td>
</tr>
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<td>(R,S)-9d</td>
<td>96(13)(^d)</td>
<td>8.0</td>
<td>91(R)</td>
<td>69</td>
<td>65.2</td>
<td>84(S)</td>
<td>89</td>
<td>3.0</td>
<td>90(R)</td>
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<tr>
<td>6</td>
<td>(R,S)-9e</td>
<td>99(27)(^d)</td>
<td>27.6</td>
<td>66(R)</td>
<td>88</td>
<td>22.9</td>
<td>65(S)</td>
<td>95</td>
<td>2.5</td>
<td>65(R)</td>
</tr>
<tr>
<td>7</td>
<td>(R)-9f</td>
<td>99(29)(^d)</td>
<td>56.6</td>
<td>75(R)</td>
<td>95</td>
<td>7.5</td>
<td>66(S)</td>
<td>98</td>
<td>2.9</td>
<td>69(R)</td>
</tr>
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</table>

\(^a\) All reactions were carried out at 60 °C in toluene with L:Rh = 4:1, substrate/Rh = 1000, 20 bar 1:1 CO/H\(_2\), and 24 h reaction time for styrene, vinyl acetate and 18 h reaction time for allyl cyanide. \(^b\) Conversions, branched/linear ratio and ee values were determined by GC analysis (Supelco's Beta Dex 225). The absolute configuration for the products 21, 24 and 27 were assigned by comparing the sign of the optical rotations with those in the
Determined by converting the aldehyde to the corresponding acid and then reacting with aniline to afford corresponding amide followed by HPLC analysis. The number in parentheses represents the conversion of a 3 h reaction.

2.2.3 Mechanistic Study of Ligand 7 in Asymmetric Hydroformylation

To explain the above observation on the ligand structure-selectivity relationship, the mechanistic catalytic cycle for Rh/7 catalyzed asymmetric hydroformylation was proposed in Scheme 2-4. Based on the mechanistic studies by Takaya and coworkers, it is believed that the Rh[(R,S)-binaphos]H(CO)2] complex exists as a single trigonal bipyramidal complex with the phosphine occupied an equatorial position and the phosphate located at an axial position which is trans to the hydrido ligand.9b Because of the structural and electronegative similarity to binaphos (as shown in Figure 2-1), ligand 7 is proposed to proceed a similar catalytic cycle as that of binaphos.

Upon mixing Rh(CO)2(acac) with ligand 7, the trigonal bipyramidal complex 29 was obtained, which dissociate a CO to form the catalytically active species 30. The main catalytic cycle starts with the coordination of alkene (represented by styrene here) preferably in the equatorial position thus affording hydrido olefin complex 31. Styrene insertion into the Rh-H bond takes place to form tetragonal alkyl rhodium complexes 32. Subsequent coordination of carbon monoxide and then migratory insertion of the alkyl group to one of the coordinated carbon monoxide yields acyl complexes 34. Followed by oxidative addition of hydrogen, tetragonal bipyramidal rhodium(II) complexes 35 was
formed, which undergoes reductive elimination to release the 2-Phenylpropan-1-ol and regenerates the catalytically active species 30 (Scheme 2-4).

Herrmann and coworkers raised a semiquantitative theretical model which can successfully elucidate the origin of stereodifferentiation in Rh-binaphos-catalyzed AHF. In this model, the insertion of alkene into the Rh-H bond of the hydrido olefin complex 31 to form tetragonal alkyl rhodium complexes 32 was believed to be the enantioselectivity-determining step. Base on CAChe MM2 calculation, we studied the key intermediate of the enantioselectivity-determining step in the hydroformylation with our ligands 7. (R,S)-7b was selected as a representative ligand and styrene represents a
typical olefin substrate herein (as shown in Scheme 2-5). On the basis of Herrmann’s model, we extrapolate that there is four possible transition states (TS I, II, III and IV, as shown in upper part of Scheme 2-5) in the process of styrene (labeled as green) insertion into the Rh-H bond of RhH(CO)[(R,S)-7b]. Due to the repulsion between the phenyl ring of styrene and the ligand backbone, TS I and TS IV represent the minor species leaving the less hindered TS II and TS III as major species. Both of two approaching manner of styrene to the Rh center, showing in TS II and TS III, afford the same configuration (R)-2-phenylpropanal. From the stick models for TS II and TS III based on CAChe MM2 calculation, it is concluded that the enantioselectivity arises from the steric repulsion between the phenyl group of styrene and one of the naphthyl fragments of (R,S)-7b (marked with black rectangle). In TS II, it is the naphthyl from naphthylamine to repulse the phenyl ring, while it is the one from phosphoramidite in TS III. This model can rationalize our experiment results well. As shown in Scheme 2-5, the ethyl group on N atom stretches back away from the plane of Rh-H bond and does not interact with the styrene at all. Thus changing the N-substituent did not exert significant influence on the enantioselectivity of phosphine-phosphoramidite ligands (Table 2-2, entries 1-3). Expanding the steric bulkiness of phsophoramidite fragment (marked as dashed rectangle in Scheme 2-5) will increase the repulsion to the phenyl ring of styrene and diminish the energy gap between the Re and Si binding of styrene to Rh center in TS II, although it is somewhat beneficial to the differentiation of two enantiofaces in TS III. The overall effect will damage the enantioselectivity of our ligands. Hereby, (R,S)-7d provided weaker enantioselectivity for all the three substrates than that of (R,S)-7b. In like manner,
(R,S)-7e, with two bulky t-butyl groups on the phosphoramidite fragment, has even worse enantioselectivity (Table 2-2, entries 4-6).

It is hard to predict the regioselectivities of the phosphine-phosphoramidite ligands with this theoretical model. Generally, the regioselectivity of hydroformylation reaction is mainly determined by the functional group of olefin, e.g. phenyl group in styrene. The higher chelation stability with the Rh centre the functional group has, the more branched aldehyde will form. In our experiment, regarding to styrene, a trend was observed that the ligand with more bulky substituent provides better regioselectivity.
Scheme 2-5: Transition States of Styrene Insertion into The Rh-H Bond of RhH(CO)[(R,S)-7b] Base on CAChe MM2 Calculation. Upper: Models for four possible transition states, TS I to TS IV. Lower: Stick models for the corresponding transition state II and III based on CAChe MM2 calculation (black rectangle represents naphthyl fragments from backbone, dashed rectangles represent naphthyl from phosphoramidite moiety).
2.2.4 Substrate Scope of Rh/7 Catalyzed Asymmetric Hydroformylation

Encouraged by the successful application of ligand 7b in the Rh-catalyzed asymmetric hydroformylation of styrene and vinyl acetate, a series of their derivatives were hydroformylated utilizing the Rh-(R,S)-7b catalyst under the optimized reaction condition. All the styrene derivatives obtained good regioselectivities and excellent enantioselectivities (up to 99 % ee, Table 2-3, entries 1-6). Especially those halogen-substituted styrene derivatives achieved high ee values with high conversion (Table 2-3, entries 2-4). It is worth noting that 98 % ee was achieved for the para-isobutyl styrene (Table 2-3, entry 6). Its aldehyde product could be oxidized into ibuprofen, one of the most widely used nonsteroidal anti-inflammatory.

As shown in Table 2-3, entries 7-12, a series of vinyl acetate derivatives were hydroformylated with this catalyst system. Remarkably, the hydroformylation of 2,2-dimethyl-propionic acid vinyl ester, bearing a bulky alkyl residue on the carboxyl group, demonstrate the highest enantioselectivity (98 % ee, Table 2-3, entry 6). In general, all of the styrene and vinyl acetate derivates achieved high regio- and enantioselectivities in Rh-7b catalyzed asymmetric hydroformylation, which make this methodology potential to industrial application.
Table 2-3: Rh-catalyzed Asymmetric Hydroformylation of Styrene and Vinyl Acetate Derivatives with \((R,S)-7b\)^a

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conv.[%]^b</th>
<th>b/l^b</th>
<th>ee[%]^c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-Me-Ph</td>
<td>98</td>
<td>7</td>
<td>99(R)</td>
</tr>
<tr>
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<td>4</td>
<td>p-Cl-Ph</td>
<td>99</td>
<td>7</td>
<td>98(R)</td>
</tr>
<tr>
<td>5</td>
<td>p-MeO-Ph</td>
<td>97</td>
<td>6</td>
<td>98(R)</td>
</tr>
<tr>
<td>6</td>
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<td>98(R)</td>
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<td>7</td>
<td>CH₃CH₂COO</td>
<td>67</td>
<td>24</td>
<td>93(S)</td>
</tr>
<tr>
<td>8</td>
<td>CH₃(CH₂)₂COO</td>
<td>53</td>
<td>16</td>
<td>94(S)</td>
</tr>
<tr>
<td>9</td>
<td>CH₃(CH₂)₆COO</td>
<td>56</td>
<td>16</td>
<td>94(S)</td>
</tr>
<tr>
<td>10</td>
<td>CH₃(CH₂)₈COO</td>
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<td>16</td>
<td>96(S)</td>
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<tr>
<td>11</td>
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<tr>
<td>12</td>
<td>PhCOO</td>
<td>69</td>
<td>24</td>
<td>93(S)</td>
</tr>
</tbody>
</table>

^a All reactions were carried out at 60 °C in benzene with L:Rh = 4:1, substrate/catalyst = 1000, 20 bar 1:1 CO/H₂, and 24 h. ^b Conversions, branched/linear ratio were determined based on \(^1\)H NMR. ^c Determined by GC analysis. The absolute configuration were assigned by comparing the sign of the optical rotations with those in the literature.\(^\text{16}\)
2.3 Conclusion

In summary, a series of hybrid phosphine-phosphoramidite ligands has been developed and systematically applied in Rh-catalyzed asymmetric hydroformylation of styrene, vinyl acetate, allyl cyanide and their derivatives with highly regio- and enantioselectivities under mild conditions. With ligand 7b, 99 % ee for styrene derivatives, 98 % ee for vinyl acetate derivatives and 96 % ee allyl cyanide were achieved, which represents the best result up to date. The relationship between the substituent and the enantioselectivity of the ligands was concluded, which was successfully rationalized by Herrmann’s theoretical model with CAChé MM2 calculation. Further understanding the origination of the selectivity of phosphine-phosphoramidite ligands and their application in other metal-catalyzed transformations are in progress in our lab.
Experimental Section

General Methods: All reactions and manipulations that were sensitive to moisture or air were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. Solvents were dried with standard procedures and degassed with N₂. Column chromatography was performed using 200-400 mesh silica gel supplied by Natland International Corp. Molecular mechanics calculations were carried out with CAChe® program (Fujitsu Ltd.). Thinlayer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. ¹H, ¹³C, and ³¹P NMR spectra were recorded in CDCl₃ or CD₂Cl₂ on Bruker Avance 400 MHz spectrometers or Varian Mercury 500 MHz FT-NMR spectrometer. Optical rotation was obtained on a Perkin-Elmer 341 MC polarimeter. HRMS were recorded on a Thermo LTQ Orbitrap hybrid mass spectrometer. GC analysis was carried out on Hewlett-Packard 7890 gas chromatography using chiral capillary columns.

Synthesis of (S)-2,2'-bistriflate-1,1'-binaphthyl (9)

To a solution of (S)-BINOL 8 (4.03 g, 14.1 mmol) in 100 mL of CH₂Cl₂ was added pyridine (40 mL) and followed by dropwise addition of triflic anhydride (5.05 mL, 30 mmol) at 0 °C. The mixture was stirred at r.t. for 6 h. After removal of the solvent, the residue was diluted with EtOAc (50 mL) and then washed with 5% aqueous HCl (50
mL), saturated NaHCO₃ (50 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated and passed through a silica gel plug (eluted with CH₂Cl₂) to give the (S)-9 (7.4 g, 95%). ¹H NMR (400 MHz, CDCl₃) δ: 7.27 (d, J = 8.5, 2H), 7.42 (ddd, J = 1.1, 6.8, 8.2, 2H), 7.59 (ddd, J = 1.0, 7.0, 8.1, 2H), 7.63 (d, J = 9.1, 2H), 8.02 (d, J = 8.2, 2 H), 8.15 (d, J = 9.1, 2 H) ; ¹³C NMR (100 MHz, CDCl₃) δ: 118.3, 119.4, 123.6, 126.8, 127.4, 128.1, 128.5, 132.1, 132.5, 133.2, 145.5.

**Synthesis of (S)-2-(Diphenylphosphiny1)-2'-[(trifluoromethanesulfonyl) oxy]-1,1'-binaphthyl (10)**

![Structure of compound 10](image)

To a mixture of (S)-9 (6.25 g, 11.74 mmol), diphenylphosphine oxide (4.59 g, 22.7 mmol), palladium diacetate (127 mg, 0.57 mmol), and 1,4-bis(diphenylphosphino)butane (dppb, 242 mg, 0.57 mmol) were added 50 mL of DMSO and diisopropylethylamine (5.85 g, 45.4 mmol), and the mixture was stirred and heated at 120 °C for 12 h. After cooling to room temperature, the solvent was removed under reduce pressure. The residue was diluted with 100 mL EtOAc, washed with water (60 mL X 2), dried over MgSO₄, and concentrated under reduced pressure. The residue was subjected column chromatography on silica gel (elution with hexane/EtOAc 1:1) to give (S)-10 as a white solid (7.5 g, 95%). ¹H NMR (400 MHz, CDCl₃) δ: 6.98-8.01 (m, 22H, Ar); ³¹P NMR (202 MHz, CDCl₃) δ: 29.2.
Synthesis of (S)-2-Cyano-2'-diphenylphosphinyl-1,1'-binaphthyl (11)

To a mixture of (S)-10 (7.05 g, 11.7 mmol), potassium cyanide (7.55 g, 116 mmol), nickel dibromide (1.13 g, 5.2 mmol), triphenylphosphine (6.04 g, 23.0 mmol) and activated zinc powder (1.05 g, 16.1 mmol) was added 70 mL of acetonitrile. The mixture was stirred and refluxed under N\textsubscript{2} for 3 h. After cooling to r. t., the mixture was diluted with EtOAc and washed with water and brine. The organic phase was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. The residue was purified with column chromatography on silica gel (elution with hexane/EtOAc, 1:3) to give (S)-11 as a white solid (5.56 g, 99%). \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 8.02 (dd, \(J = 8.6, 2.0\) Hz, 1H), 7.94 (d, \(J = 8.2\) Hz, 1H), 7.84 (dd, \(J = 8.2, 5.3\) Hz, 1H), 7.7–7.1 (m, 16H), 7.02 (t, \(J = 9.6\) Hz, 2H); \(^{31}\)P NMR (202 MHz, CDCl\textsubscript{3}) \(\delta\): 28.2.

Synthesis of (S)-2-Carbamoyl-2'-diphenylphosphinyl-1,1'-binaphthyl (12)

To a stirred cooled solution of (S)-11 (5.00 g, 10.4 mmol) in DMSO (50 mL) were added 30\% H\textsubscript{2}O\textsubscript{2} (25 mL) dropwisely and then anhydrous K\textsubscript{2}CO\textsubscript{3} (28.8 g) in an ice bath. The mixture was allowed to warm up to r.t. (warning: exothermic process). After 30 min,
the mixture was added distilled water (20 mL) and DMSO (20 mL) in an ice bath, and then stirred at r.t. overnight. The reaction mixture was diluted with EtOAc and quenched with saturated NH₄Cl (50 mL). The organic phase was washed twice with H₂O and brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with EtOAc) to afford (S)-12 as a white solid (5.11 g, 95%). ¹H NMR (400 MHz, CDCl₃) δ: 9.45 (bs, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.8–7.7 (m, 3H), 7.64 (d, J = 7.8 Hz, 1H), 7.6–7.4 (m, 5H), 7.3–7.2 (m, 1H), 7.2–7.0 (m, 5H), 7.0–6.9 (m, 2H), 6.64 (t, J = 7.0 Hz, 1H), 6.33 (d, J = 8.4 Hz, 1H), 5.52 (bs, 1H); ³¹P NMR (202 MHz, CDCl₃) δ: 30.8.

**Synthesis of (S)-2-Methoxycarbonylamino-2'-diphenylphosphinyl-1,1'-binaphthyl (13)**

![Chemical structure](image)

To a solution of 25 wt% sodium methoxide in methanol (11.1 mL, 48.7 mmol) was added methanol (80 mL). The solution was cooled to −78°C and bromine (0.92 mL, 17.9 mmol) was added dropwise with vigorous stirring. After stirring at −78°C for 15 min, a solution of (S)-12 (4.03 g, 8.1 mmol) in methanol (72 mL) and dioxane (72 mL) was added dropwise for 30 min. The reaction mixture was stirred at r.t. for 1 h and then stirred at 55°C for 1 h. After being cooled to r.t., the mixture was diluted with EtOAc and quenched with saturated NH₄Cl. The organic layer was washed with brine, dried over
Na₂SO₄, and concentrated under reduced pressure. The residue was chromatographed on silica gel (elution with hexane/EtOAc, 1:2) to give (S)-13 as white solid (3.60 g, 83%).

¹H NMR (400 MHz, CDCl₃) δ: 8.74 (bs, 1H), 7.9–7.6 (m, 5H), 7.67 (d, J = 8.8 Hz, 1H), 7.6–7.4 (m, 6H), 7.3–7.1 (m, 4H), 7.09 (d, J = 8.8 Hz, 1H), 6.95 (t, J = 7.2 Hz, 1H), 6.82 (t, J = 7.0 Hz, 1H), 6.7–6.6 (m, 2H), 6.51 (d, J = 6.8 Hz, 1H), 3.05 (bs, 3H); ³¹P NMR (202 MHz, CDCl₃) δ: 28.2.

_Synthesis of (S)-2-Methylamino-2’-diphenylphosphino-1,1'-binaphthyl (14a)_

To a solution of (S)-13 (1.80 g, 3.40 mmol) in THF (90 mL) was added 2 M borane-dimethyl sulfide complex in THF (13.6 mL, 27.2 mmol) at 0°C, the mixture was refluxed under N₂ for 16 h. After cooling to r.t., the mixture was diluted with EtOAc and quenched with saturated aqueous NH₄Cl. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. To the residue was added 120 mL of diethylamine and the reaction mixture was stirred at r.t. for 30 min. After removal of diethylamine, the residue was chromatographed on silica gel (elution with hexane/EtOAc, 20:1 to 10:1) to give (S)-14a as a yellow solid (1.10 g, 69%). ¹H NMR (400 MHz, CDCl₃) δ: 7.9–7.8 (m, 3H), 7.73 (d, J = 8.3 Hz, 1H), 7.5–7.4 (m, 2H), 7.3–6.9 (m, 15H), 6.70 (d, J = 8.3 Hz, 1H), 3.04 (bs, 1H), 2.37 (s, 3H). ³¹P NMR (202 MHz, CDCl₃) δ: –13.8.
Synthesis of (S)-2-Ethylamino-2'-diphenylphosphino-1,1'-binaphthyl (14b)

To a solution of (S)-13 (2.00 g, 3.80 mmol) in methanol (75 mL) was added a 40% KOH solution (40 mL) and the mixture was refluxed for 2 h. After being cooling to r.t., the mixture was diluted with EtOAc. The organic phase was washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude (S)-2-Amino-2'-diphenylphosphinyl-1,1'-binaphthyl (1.79 g, quantitative) was used for next step without further purification. $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$: –13.8.

To a solution of above amine (1.79 mg, 3.80 mmol) in 75 mL of CH$_2$Cl$_2$ were added pyridine (0.37 mL, 4.57 mmol) and acetyl chloride (0.31 mL, 4.19 mmol) at 0°C and the mixture was stirred at rt for 1 h. The mixture was diluted with CH$_2$Cl$_2$. The organic phase was washed with saturated NH$_4$Cl and brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was passed through a silica gel plug (elution with hexane/EtOAc, 3:1) to afford (S)-2-Acetylamino-2'-diphenylphosphinyl-1,1'-binaphthyl (1.96 g, 99%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 9.73 (s, 1H), 8.0–7.9 (m, 4H), 7.8–7.6 (m, 2H), 7.6–7.4 (m, 6H), 7.3–7.1 (m, 5H), 7.0–6.9 (m, 1H), 6.8–6.7 (m, 1H), 6.7–6.6 (m, 1H), 6.53 (d, $J = 8.3$ Hz, 1H), 1.93 (s, 3H). $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$: 29.6.

To a solution of above acetylamino (1.27 g, 2.50 mmol) in THF (60 mL) was added 2M borane-dimethyl sulfide complex in THF (6.20 mL, 12.4 mmol) at 0°C, the
mixture was refluxed for 16 h. After cooling to r.t., the mixture was diluted with EtOAc and quenched with saturated NH₄Cl. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. To the residue was added 82.0 mL of diethylamine and the reaction mixture was stirred at r.t. for 3 h. After removal of diethylamine, the residue was chromatographed on silica gel (elution with hexane/EtOAc, 20:1) to give (S)-14b as a yellow solid (0.83 g, 69%). ¹H NMR (400 MHz, CDCl₃) δ: 8.0–7.8 (m, 3H), 7.74 (d, J = 8.5 Hz, 1H), 7.5–7.4 (m, 2H), 7.3–6.9 (m, 16H), 6.59 (d, J = 8.5 Hz, 1H), 3.07 (m, 2H), 2.9–2.7 (m, 1H), 0.78 (t, J = 7.0 Hz, 3H). ³¹P NMR (202 MHz, CDCl₃) δ: –13.8.

**Synthesis of (S)-2-Benzylamino-2'-diphenylphosphino-1,1'-binaphthyl (14c)**

![Chemical Structure](image)

The synthesis of (S)-14c is following the same procedure as (S)-14b except using benzoyl chloride instead of acetyl chloride.

(S)-2-Benzoylamino-2'-diphenylphosphinyl-1,1'-binaphthyl (99%). ¹H NMR (400 MHz, CDCl₃) δ: 10.60 (s, 1H), 8.0–7.8 (m, 7H), 7.71 (d, J = 8.0 Hz, 1H), 7.8–7.1 (m, 15H), 7.0–6.9 (m, 1H), 6.9–6.7 (m, 1H), 6.7–6.6 (m, 1H), 6.51 (d, J = 8.0 Hz, 1H). ³¹P NMR (202 MHz, CDCl₃) δ: 30.2.

(S)-14c as a yellow solid (82%). ¹H NMR (400 MHz, CDCl₃) δ: 7.9–7.8 (m, 2H), 7.82 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.6–7.4 (m, 2H), 7.4–7.0 (m, 19H),
7.0–6.9 (m, 1H), 6.62 (d, $J = 8.4$ Hz, 1H), 4.16 (d, $J = 15.2$ Hz, 1H), 3.98 (d, $J = 15.2$ Hz, 1H), 3.68 (bs, 1H). $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$: −13.4.

**Synthesis of (R)-2-Acetylamino-2'-Hydroxy-1,1'-binaphthyl (17)**

To a solution of (R)-NOBIN 16 (2.85 g, 10.0 mmol) in dry pyridine (40 mL) was slowly added acetyl chloride (1.60 mL, 11.0 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 8 h. The reaction mixture was then poured into icy water (40 mL) and extracted with dichloromethane (3 x 50 mL). The organic phase was successively washed with 5% aqueous HCl solution (50 mL), saturated aqueous NaHCO$_3$ solution (50 mL) and water (50 mL), and then dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluted with toluene/ethyl acetate 2:1) to give N,O-diacetate intermediate. The diacetate was dissolved in dry methanol (300 mL). To the resulting solution was added catalytic amount of NaOMe (20 mg). The reaction mixture was stirred at r.t. for 3 h. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluted with hexane/ethyl acetate 1:1) to give (R)-17 (3.10 g, 95 %): $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 8.44 (d, $J = 8.86$ Hz, 1H), 8.04-7.90 (m, 4H), 7.47-7.23 (m, 5H), 7.11 (d, $J = 8.42$ Hz, 1H), 6.99 (m, 2H), 5.79 (bs, 1H), 1.77 (s, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 169.4, 152.6, 136.0, 133.6, 133.2,
Synthesis of (R)-Trifluoro-methanesulfonic Acid 2'-Acetylamino-[1,1']binaphthalenyl-2-yl Ester (18)

To a solution of (R)-17 (2.55 g, 7.80 mmol) in CH₂Cl₂ (50 mL) and pyridine (0.70 mL, 8.60 mmol) was slowly added trifluoromethanesulfonic anhydride (1.45 mL, 8.60 mmol) at 0 °C. After being allowed to warm to room temperature and stirred for 3 h, the reaction mixture was then diluted with CH₂Cl₂ (100 mL). The diluted solution was washed with aqueous 5% HCl (2 x 30 mL), saturated NaHCO₃ (25 mL), and water (25 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluted with hexane/EtOAc 2:1) to give (R)-18 as a yellow solid (3.26 g, 91%): ¹H NMR (300 MHz, CD₂Cl₂) δ: 8.46 (d, J = 8.8 Hz, 1H), 8.23 (d, J = 9.1 Hz, 1H), 8.10 (t, J = 8.8 Hz, 2H), 7.99 (d, J = 8.1 Hz, 1H), 7.67-7.62 (m, 2H), 7.50-7.43 (m, 2H), 7.38-7.29 (m, 2H), 7.08 (d, J = 8.43 Hz, 1H), 6.97 (bs, 1H); ¹³C NMR (75 MHz, CD₂Cl₂) δ: 168.7, 146.0, 135.8, 133.4, 133.2, 132.7, 132.3, 131.4, 130.3, 128.9, 128.8, 128.6, 128.1, 127.3, 126.7, 126.4, 125.7, 125.2, 125.0, 122.5, 120.7, 119.9, 119.1, 116.5, 112.2, 24.3.
Synthesis of \((R)-2\text{-Acetylamino-}2'\text{-diphenylphosphinyl-1,1'}\text{-binaphthyl}\) (19)

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\]

To a mixture of \((R)-18\) (3.15 g, 6.85 mmol), diphenylphosphine oxide (3.00 g, 15.00 mmol), palladium(II) acetate (77 mg, 0.34 mmol) and dppb (144 mg, 0.34 mmol) were added DMSO (150 mL) and diisopropylethylamine (4.50 mL, 59.0 mmol) under nitrogen. The reaction mixture was stirred at 120 °C for 14 h. After cooling to 80 °C, the solvent was removed under reduced pressure. To the residue was added 5% aqueous HCl solution (150 mL). The product was extracted with dichloromethane (3 x 150 mL). The combined extracts were washed with 1% aqueous HCl (150 mL) and water (150 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluted with hexane/EtOAc 4:1) to afford the \((R)-19\) as a colorless solid (2.94 g, 84%). ¹H NMR (360 MHz, CD₂Cl₂) δ: 9.86 (s, 1H), 8.05-7.96 (m, 4H), 7.75 (q, \(J = 7.3\) Hz, 2H), 7.63-7.52 (m, 6H), 7.28-7.23 (m, 4H), 7.13 (d, \(J = 8.6\) Hz, 1H), 7.01 (t, \(J = 7.9\) Hz, 1H), 6.84 (t, \(J = 7.3\)Hz, 1H), 6.73-6.70 (m, 2H), 6.56 (d, \(J = 8.4\) Hz, 1H), 1.91 (s, 3H). ¹³C NMR (91MHz, CD₂Cl₂) δ: 169.29, 141.49, 141.40, 136.43, 135.37, 135.35, 133.68, 133.36, 132.74, 132.37, 132.31, 132.27, 131.30, 130.51, 130.48, 130.03, 129.92, 129.59, 129.31, 129.07, 128.94, 128.74, 128.70, 128.61, 128.24, 128.18, 128.04, 127.94, 127.61, 127.58, 127.52, 127.47, 126.84, 126.01, 125.28, 23.78. ³¹P NMR (146 MHz, CH₂Cl₂) δ: 28.5.
Synthesis of (R)-2-Ethylamino-2'-diphenylphosphino-1,1'-binaphthyl (14b)

The synthesis of (R)-14b is following the same procedure as (S)-14b. $^1$H NMR (360 MHz, CD$_2$Cl$_2$) $\delta$: 7.91 (t, $J = 8.92$ Hz, 3H), 7.77 (d, $J = 8.01$ Hz, 1H), 7.54-7.744 (m, 2H), 7.33-7.16 (m, 11H), 7.12 (t, $J = 7.40$ Hz, 1H), 7.07-7.01 (m, 3H), 6.65 (d, $J = 8.47$ Hz, 1H), 3.21, (m, 1H), 3.07-3.00 (m, 1H), 2.81-2.72 (m, 1H), 0.76 (t, $J = 7.11$ Hz, 3H); $^{13}$C NMR (91MHz, CD$_2$Cl$_2$) $\delta$: 144.81, 144.78, 142.62, 142.24, 138.65, 138.50, 138.12, 137.65, 134.79, 134.18, 133.96, 133.63, 133.42, 133.35, 131.34, 129.91, 128.97, 128.91, 128.90, 128.81, 128.66, 128.59, 128.56, 128.47, 128.31, 127.60, 127.34, 127.19, 126.77, 126.74, 126.57, 124.31, 121.79, 116.24, 116.14, 113.92. 38.68, 15.17; $^{31}$P NMR (146 MHz, CH$_2$Cl$_2$) $\delta$: −14.2.

A Typical Procedure for The Preparation of Phosphorochloridite 15.

To a mixture of (R)-BINOL (1.75 g, 6.0 mmol) and Phosphorus trichloride (12.5 g, 90.0 mmol) was added a drop of N-methylpyrrolidone (NMP) (catalytic amount) at room temperature under nitrogen. The resulting solution was heated at reflux for 6 h. After cooling to room temperature, the excess phosphorus trichloride was removed under
reduced pressure. Azeotropic evaporation of the trace amount of phosphorus trichloride in the residue with degassed toluene twice (2 X 10 mL) under reduced pressure afforded the (R)-15a as white foam in quantitative yield (2.2 g). The crude product was pure enough and was used in the next step without further purification: $^1$H NMR (360 MHz, CD$_2$Cl$_2$) $\delta$: 8.07-7.98 (m, 4H), 7.57-7.46 (m, 4H), 7.39-7.29 (m, 4H); $^{13}$C NMR (90 MHz, CD$_2$Cl$_2$) $\delta$: 148.2 (d, $J = 3.1$ Hz), 147.6 (d, $J = 4.5$ Hz), 133.0 (d, $J = 1.7$ Hz), 132.7 (d, $J = 1.6$ Hz), 132.4, 131.9, 131.4, 130.5, 128.9 (d, $J = 0.9$ Hz), 127.2, 127.1, 126.9, 126.1, 125.9, 124.7 (d, $J = 5.7$ Hz), 123.4 (d, $J = 2.3$ Hz), 121.9 (d, $J = 1.2$ Hz), 121.4 (d, $J = 1.6$ Hz). $^{31}$P NMR (146 MHz, CD$_2$Cl$_2$) $\delta$: 178.8.

(S)-3,3'-Dimethyl-1,1'-binaphthalene-2,2'-dioxychlorophosphine (15d): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.4-7.8 (m, 6H), 7.2-7.4 (m, 2H), 6.9-7.1 (m, 2H), 2.27 (s, 3H), 2.04 (s, 3H); $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$: 175.5.

3,3',5,5'-Tetra(tert-butyl)-2,2'-biphenol Phosphorochloridite (15f): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.50 (d, $J = 2.4$ Hz, 2H), 7.22 (d, $J = 2.4$ Hz, 2H), 1.51 (s, 18H), 1.39 (s, 18H); $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$: 175.5.

Synthesis of (S) 3,3'-Di-tert-butyl-5,5',6,6'-tetramethyl-2,2'-bisphenol Phosphorobromidite (15e)$^{5a,20}$
To a solution of (S)-3,3'-di-tert-butyl-5,5',6,6'-tetramethyl-biphenyl-2,2'-diol [(S)-BIPHEN-H2] (1.01 g, 2.86 mmol) in 25 mL of toluene were added NEt₃ (0.81 mL, 5.83 mmol) and PBr₃ (0.28 mL, 2.9 mmol) at room temperature. The reaction mixture was then stirred for 12 h. The suspension was filtered, and the filtrate was evaporated to give (S)-15e as a white solid (0.85 g, 68 % yield). ¹H NMR (400 MHz, CDCl₃) δ: 7.18 (s, 1H), 7.08 (s, 1H), 1.93 (s, 3H), 1.92 (s, 3H), 1.57 (s, 3H), 1.56 (s, 3H), 1.48 (s, 9H), 1.39 (s, 9H); ³¹P NMR (202 MHz, CDCl₃) δ: 183.2.

A Typical Procedure for The Preparation of Phosphine-phosphoramidite Ligand 7:

**Synthesis of Ligand (S,R)-7a**

To a solution of (S)-14a (480 mg, 1.0 mmol) in anhydrous THF (10 mL) at -78 °C under N₂ atmosphere was added dropwise nBuLi (1.2 mmol, 0.48 mL of 2.5 M hexane solution). The reaction mixture was turned out to a deep red solution and stirred for 4 h at that temperature. Then (R)-15a (454 mg, 1.3 mmol) in THF (6 mL) was added dropwise. After addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent were removed under vacuum. To the residue was added CH₂Cl₂ (5 mL) and the mixture was filtered to remove the inorganic salt. The filtration was concentrated and subjected to flash chromatography on silica gel (eluted with
hexane/EtOAc/NEt₃ 100:10:1) to afford pure ligand (S,R)-7a as white solid (257 mg, 33 %). \([\alpha]_D^{20} = -32.6 (c = 0.3, \text{CHCl}_3);^1\text{H} \text{NMR (500 MHz, CDCl}_3) \delta: 8.04-8.01 (m, 3H), 7.85 (t, J = 8.5 Hz, 2H), 7.78 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 9.0 Hz, 1H), 7.61-7.57 (m, 2H), 7.38-6.93 (m, 21H), 6.59 (dd, J = 8.5, 7.0 Hz, 1H), 6.49 (d, J = 8.5 Hz, 1H), 6.31 (d, J = 8.5 Hz, 1H), 2.45 ppm (s, 3H); \(^{13}\text{C} \text{NMR (125 MHz, CDCl}_3) \delta: 150.45, 150.41, 149.61, 142.76, 142.49, 138.60, 138.49, 137.88, 137.79, 136.63, 135.25, 135.07, 134.08, 133.16, 133.03, 132.65, 131.61, 131.50, 130.73, 130.28, 129.94, 129.87, 128.84, 128.48, 128.31, 128.28, 128.20, 128.02, 127.75, 127.56, 127.42, 127.24, 127.16, 126.99, 126.53, 126.09, 125.69, 125.35, 124.86, 124.64, 124.12, 124.08, 122.28, 122.20, 35.67, 35.64 ppm; \(^{31}\text{P} \text{NMR (202 MHz, CDCl}_3) \delta: 141.09 (d, J = 45.2 Hz), -12.67 ppm (d, J = 45.2 Hz); \text{HRMS (ESI): } m/z: \text{calcd for } C_{53}H_{38}NO_2P_2 ([M+H^+] ): 782.2578; \text{found: } 782.2374.

Ligands 7b-f were synthesized in moderate yields following the above procedure. Their characterization data are summarized as following.

(L,R)-7b: Yield = 38 %; white solid; \([\alpha]_D^{20} = -18.3 (c = 0.4, \text{CHCl}_3);^1\text{H} \text{NMR (400 MHz, CDCl}_3) \delta: 8.07-7.98 (m, 3H), 7.90 (t, J = 7.3 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H), 7.64-7.57 (m, 4H), 7.38-6.99 (m, 16H), 6.96 (t, J = 6.8 Hz, 2H), 6.85 (t, J = 7.1 Hz, 2H), 6.55 (t, J = 7.7 Hz, 1H), 6.38-6.29 (m, 2H), 2.75-2.67 (m, 1H), 2.37-2.29 (m, 1H), 0.65 ppm (t, J = 7.0 Hz, 3H); \(^{13}\text{C} \text{NMR (100 MHz, CDCl}_3) \delta: 150.29, 150.22, 149.94, 142.34, 141.95, 138.57, 138.36, 138.27, 138.20, 135.44, 135.14, 134.10, 133.57, 133.36, 131.68, 130.50, 129.88, 129.11, 128.66, 128.59, 128.55,
128.49, 128.46, 128.42, 128.30, 128.12, 127.56, 127.19, 127.12, 127.03, 126.66, 126.29,
126.17, 125.71, 125.53, 125.06, 124.76, 122.49, 122.24, 122.21, 41.05, 14.99 ppm; $^{31}$P
NMR (162 MHz, CDCl$_3$) δ: 141.00 (d, $J = 59.1$ Hz), -13.48 ppm (d, $J = 59.1$ Hz); HRMS
(ESI): $m/z$: calcd for C$_{54}$H$_{40}$NO$_2$P$_2$ ([M+H$^+$]): 796.2534; found: 796.2536.

(S,R)-7c: Yield = 42 %; white solid; $[\alpha]^D_{20} = +32.5$ (c = 0.3, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ: 8.17 (d, $J = 8.5$ Hz, 1H), 8.15 (d, $J = 8.0$ Hz, 1H), 7.97 (d, $J = 8.0$ Hz, 1H), 7.92 (d, $J = 8.0$ Hz, 1H), 7.74-7.60 (m, 5H),
7.43-7.01 (m, 23H), 6.87-6.83 (m, 2H), 6.79-6.75 (m, 2H), 6.45-6.42 (m, 1H), 6.24 (d, $J$
= 8.5 Hz, 1H), 5.93 (d, $J = 8.5$ Hz, 1H), 3.82 (d, $J = 14.5$ Hz, 1H), 3.21 (d, $J = 14.5$ Hz,
1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 150.09, 150.05, 149.84, 142.04, 141.91, 138.75,
128.24, 127.92, 137.81, 135.61, 135.42, 133.97, 133.56, 133.43, 132.01, 131.81, 131.75,
131.61, 130.72, 130.50, 130.35, 129.87, 129.81, 128.83, 128.74, 128.56, 128.48, 128.40,
128.37, 128.33, 128.21, 128.11, 128.04, 127.89, 127.84, 127.79, 127.40, 127.23, 127.20,
127.04, 126.88, 126.71, 126.08, 126.03, 125.32, 124.88, 124.63, 122.78, 122.55, 122.10,
51.32 ppm; $^{31}$P NMR (202 MHz, CDCl$_3$) δ: 138.41 (d, $J = 78.6$ Hz), -11.86 ppm (d, $J$
= 78.6 Hz); HRMS (ESI): $m/z$: calcd for C$_{59}$H$_{42}$NO$_2$P$_2$ ([M+H$^+$]): 858.2691; found:
858.2692.
(R,S)-7d: Yield = 41 %; white solid; [$\alpha$]$_{D}^{20}$ = $-15.9$ ($c = 0.1$, CHCl$_3$); $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$: 8.04-7.96 (m, 3H), 7.86-7.79 (m, 3H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 8.4$ Hz, 1H), 7.53-7.45 (m, 2H), 7.39-7.28 (m, 5H), 7.26-7.05 (m, 11H), 6.96-6.93 (m, 2H), 6.86-6.81 (m, 2H), 6.61-6.57 (m, 1H), 6.33 (d, $J = 8.4$ Hz, 1H), 2.94-2.83 (m, 1H), 2.58 (s, 3H), 2.50-2.45 (m, 1H), 1.66 (s, 3H), 0.70 ppm (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$) $\delta$: 150.19, 150.12, 149.84, 142.23, 141.90, 138.93, 138.61, 138.57, 138.34, 137.72, 135.86, 135.34, 135.12, 134.41, 134.11, 133.94, 133.75, 133.74, 132.18, 132.01, 131.75, 131.68, 131.23, 131.07, 130.80, 130.06, 129.49, 129.09, 128.91, 128.58, 128.48, 128.29, 128.21, 127.93, 127.64, 127.29, 127.11, 127.02, 126.66, 125.80, 125.56, 125.32, 125.23, 125.07, 124.73, 121.81, 41.54, 17.66, 14.76 ppm; $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) $\delta$: 139.00 (d, $J = 61.6$ Hz), -14.60 ppm (d, $J = 61.6$ Hz); HRMS (ESI): m/z: calcd for C$_{56}$H$_{44}$NO$_2$P$_2$ ([M+H$^+$]): 824.2847; found: 824.2843.

(R,S)-7e: Yield = 38 %; white solid; [$\alpha$]$_{D}^{20}$ = +91.7 ($c = 0.5$, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.98 (d, $J = 8.8$ Hz, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.89 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.72 (d, $J = 8.8$ Hz, 1H), 7.63 (dd, $J = 8.4$, 2.4 Hz, 1H), 7.50-7.46 (m, 1H), 7.24-7.12 (m, 6H), 7.06-6.87 (m,
9H), 6.65 (t, J = 8.0 Hz, 1H), 3.58-3.50 (m, 1H), 2.80-2.73 (m, 1H), 2.23 (s, 3H), 2.20 (s, 3H), 1.78 (s, 3H), 1.76 (s, 3H), 1.34 (s, 9H), 0.81 (t, J = 7.2 Hz, 3H), 0.74 ppm (s, 9H); 
$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 148.95, 148.84, 147.74, 147.69, 142.72, 142.39, 138.85, 138.69, 138.46, 137.80, 137.77, 136.43, 135.12, 134.89, 134.57, 134.31, 134.05, 133.68, 133.29, 133.23, 133.13, 133.07, 131.80, 131.73, 131.25, 131.05, 130.76, 129.55, 129.38, 128.13, 128.06, 128.03, 127.72, 127.64, 127.46, 127.25, 127.20, 126.64, 126.55, 125.75, 125.15, 124.70, 40.05, 34.63, 34.07, 31.29, 31.26, 30.05, 20.19, 16.80, 16.31, 13.06 ppm; 
$^{31}$P NMR (162 MHz, CDCl$_3$) δ: 130.50 (d, J = 97.2 Hz), -14.89 ppm (d, J = 97.2 Hz); 
HRMS (ESI): m/z: calcd for C$_{58}$H$_{60}$NO$_2$P$_2$ ([M+H$^+$]): 864.4099; found: 864.4105.

(R)-7f: Yield = 52 %; white solid; [α]$_{D}^{20}$ = +40.7 (c = 0.5, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.91 (d, J = 7.2 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.50 (dd, J = 7.2, 2.8 Hz, 1H), 7.39 (t, J = 7.2 Hz, 1H) 7.24-7.00 (m, 11H), 6.97-6.93 (m, 4H), 6.85 (t, J = 7.6 Hz, 2H), 6.51-6.47 (m, 1H), 6.27 (d, J = 8.4 Hz, 1H), 3.39-3.32 (m, 1H), 3.06-2.97 (m, 1H), 1.24 (s, 9H), 1.23 (s, 9H), 1.04-0.98 (m, 18H), 0.82 ppm (t, J = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 147.50, 147.40, 146.82, 146.77, 144.32, 144.26, 143.68, 143.63, 138.82, 138.49, 137.93, 137.77, 136.99, 136.85, 133.97, 133.74, 133.48, 133.42, 133.12, 132.29, 132.22, 132.02, 131.97, 131.85, 131.80, 131.48, 130.24, 129.84, 129.73, 128.01, 127.79, 127.24, 127.05, 126.96, 126.87, 126.79, 126.68, 126.63, 126.39, 126.19, 126.14, 125.95, 125.77, 125.40,
125.04, 124.28, 124.14, 123.98, 122.77, 122.74, 37.77, 34.09, 33.67, 33.53, 33.45, 30.53, 30.49, 29.73, 29.34, 20.43 ppm; $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$: 136.29 (br), -14.93 ppm (d, $J = 62.4$ Hz); HRMS (ESI): $m/z$: calcd for C$_{62}$H$_{68}$NO$_2$P$_2$ ([M+H$^+$]): 920.4725; found: 920.4749.

**General Procedure for Asymmetric Hydroformylation:**

In a glovebox filled with nitrogen, to a 2 mL vial equipped with a magnetic bar was added ligand 7 (0.004 mmol), Rh(acac)(CO)$_2$ (0.001 mmol in 0.10 mL solvent), dodecane (50 $\mu$L, as a GC internal standard, if applicable) and substrate (1.0 mmol), additional solvent was charged to bring the total volume of the reaction mixture to 1.0 mL. After stirring for 10 min, the vial was transferred into an autoclave and taken out of the glovebox. Carbon monoxide (10 atm) and dihydrogen (10 atm) were charged in sequence. The reaction mixture was stirred at 60 $^\circ$C (oil bath) for 24 h. The reaction was cooled and the pressure was carefully released in a well ventilated hood. For analysis of the products of styrene and vinyl acetate, the conversion and regioselectivity were determined by $^1$H NMR spectroscopy of the crude reaction mixture without evaporation of the solvent. The enantiomeric excesses were determined following the reported method with a Supelco’s Beta Dex 225 column.$^{5b}$ The absolute configuration of styrene and vinyl acetate product were assigned by comparing the sign of the optical rotation with that of (R)-2-phenylpropan-1-ol or literature data.$^{9a}$ For analysis of the products of allyl cyanide, the conversion and regioselectivity were determined by GC with a Supelco’s Beta Dex 120 column.$^8$ The enantiomeric excesses of product 27 was determined by oxidation with Jones reagent to afford the corresponding carboxylic acid,
followed by reacting with aniline to give the corresponding amide which was analyzed by HPLC (Column: Chiralcel AS; solvent: hexane/iPrOH = 80:20; flow: 1.0 mL/min; 254 nm; (S) enantiomer: $t_R = 7.75$ min, (R) enantiomer: $t_R = 9.74$ min). For styrene and vinyl acetate derivatives, the conversion and regioselectivity were determined by $^1$H NMR spectroscopy from the crude reaction mixture. The enantiomeric excesses of the hydroformylation products of styrene derivatives were reduced into alcohols and then determined by GC with Supelco’s Beta Dex 225 column, while the ee values of the products of vinyl acetate derivatives were determined directly by GC with Supelco’s Beta Dex 225 column.

**Determination of The Enantiomeric Excess of Hydroformylation Products of Allyl Cyanide:**

The ee of product 3-methyl-4-oxobutanenitrile (27) was determined by oxidation with Jones reagent as follows. The hydroformylation reaction mixture was diluted in acetone (5 mL) and cooled to 0 °C. Jone’s reagent (1 mL) was added dropwise. The mixture was stirred at room temperature for 1 h, then H$_2$O (8 mL) was added. The solution was extracted with CH$_2$Cl$_2$ (10 mL) and the organic layer was dried over Na$_2$SO$_4$ and concentrated to afford the corresponding carboxylic acid. The acid was dissolved in THF (2 mL). To this solution was added aniline (0.1 mL), DMAP (8 mg) and DCC (220 mg). The reaction mixture was stirred for 30 min, and then filter through celite. The filtrate was pass a fast chromatography on silica gel to yield the branched amide (36) and linear amide (37). 36 was analyzed by HPLC (Column: Chiralcel AS; solvent:
hexane/iPrOH = 80:20; flow: 1.0 mL/min; 254 nm; (S) enantiomer: \( t_R = 7.75 \) min, (R) enantiomer: \( t_R = 9.74 \) min).

Scheme 2-7: The Derivation of Hydroformylation Products of Allyl Cyanide.

3-cyano-2-methyl-N-phenylpropanamide (36): \([\alpha]_D^{20} = +7.5\) (c = 0.5, CHCl3) at 96 % ee; \(^1\)H NMR (400 MHz, CDCl3) \( \delta \): 8.06 (s, 1H), 7.44 (d, \( J = 7.72 \) Hz, 2H), 7.23 (t, \( J = 7.56 \) Hz, 2H), 7.04 (t, \( J = 7.40 \) Hz, 1H), 2.73 (q, \( J = 6.96 \) Hz, 1H), 2.63 (dd, \( J = 16.72, 6.6 \) Hz, 1H), 2.47 (dd, \( J = 16.72, 6.64 \) Hz, 1H), 1.31 ppm (d, \( J = 6.88 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl3) \( \delta \): 171.3, 137.5, 129.0, 124.8, 120.3, 118.4, 38.5, 21.3, 17.8 ppm.

4-cyano-N-phenylbutanamide (37): \(^1\)H NMR (400 MHz, CDCl3) \( \delta \): 7.77 (s, 1H), 7.44 (d, \( J = 7.60 \) Hz, 2H), 7.24 (t, \( J = 7.64 \) Hz, 2H), 7.03 (t, \( J = 7.40 \) Hz, 1H), 2.46 (t, \( J = 7.00 \) Hz, 2H), 2.43 (t, \( J = 6.96 \) Hz, 2H), 1.99 ppm (tt, \( J = 7.00, 6.92 \) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl3) \( \delta \): 168.3, 136.7, 128.0, 123.5, 119.0, 118.3, 33.9, 19.9, 15.6 ppm.
Determination of The Enantiomeric Excess of Hydroformylation Products of Styrene Derivatives:

A portion of the reaction mixture was diluted with MeOH (2 mL) and cooled to 0 °C. To the mixture was added NaBH₄ (40 mg) in portion. The reaction mixture was allowed to stir at 0 °C for 2 h. Then water (5 mL) was added dropwise to quench the excess NaBH₄. To the resulting mixture was then added hexane (2 mL) and EtOAc (2 mL). The mixture was vigorously stirred for 5 min. The organic phase was separated, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel to get the reduced alcohol product, which was analyzed by chiral GC (Supelco β-dex 225) to determine the enantiomeric excess.

For 2-(4-Isobutyl-phenyl)-propionaldehyde, a portion of the reaction mixture was diluted with acetone (10 mL) and 1 ml of Jones reagent was added. The solution was allowed to stir at room temperature for 1 h. To the resulting green mixture was added water (10 mL). The resulting mixture was stirred for 5 min and extracted with CH₂Cl₂ (10 mL). The combined organic layer was dried over Na₂SO₄ and concentrated. The residue was subjected to column chromatography on silica gel to get the acid product which was analyzed by Chiral GC (Supelco β-120) to determine the enantiomeric excess.

NMR and Chiral GC Analysis of Hydroformylation Products of Styrene Derivatives and Their Reduction Products:
2-Phenyl-propionaldehyde. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 9.69 (d, $J = 1.3$ Hz, 1H), 7.43-7.38 (m, 2H), 7.35-7.29 (m, 1H), 7.26-7.16 (m, 2H), 3.65 (q, $J = 7.1$ Hz, 1H), 1.45 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 201.4, 138.4, 129.3, 128.7, 127.8, 53.3, 14.8.

Supelco’s Beta Dex 225 column, Temperature program: 100 ºC for 5 min, then 4 ºC/min to 160 ºC; Flow rate: 1.0 mL/min, $t_{(major)} = 12.4$ min, $t_{(minor)} = 12.5$ min.

2-(4-Fluoro-phenyl)-propionaldehyde. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 9.66 (d, $J = 1.3$ Hz, 1H), 7.23-7.18 (m, 2H), 7.11-7.06 (m, 2H), 3.64 (q, $J = 7.1$ Hz, 1H), 1.42 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 201.1, 162.5 (d, $J = 245$ Hz), 134.2 (d, $J = 3.1$ Hz), 130.4 (d, $J = 8.1$ Hz), 116.1 (d, $J = 21.5$ Hz), 52.5, 14.9.

2-(4-Fluoro-phenyl)-propan-1-ol. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 7.24-7.20 (m, 2H), 7.05-7.00 (m, 2H), 3.65 (d, $J = 6.78$ Hz, 2H), 2.92 (m, 1H), 1.38 (bs, 1H), 1.24 (d, $J = 7.03$ Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 161.9 (d, $J = 243.2$ Hz), 140.2 (d, $J = 3.5$ Hz), 129.3 (d, $J = 7.9$ Hz), 115.4 (d, $J = 21.1$ Hz), 68.8, 42.1, 17.9.

Supelco’s Beta Dex 225, 105ºC, 1mL/min, $t_{(major)} = 38.1$ min, $t_{(minor)} = 46.8$ min.
**2-(2-Fluoro-phenyl)-propionaldehyde.** $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 9.71 (d, $J = 1.65$ Hz, 1H), 7.35-7.28 (m, 1H), 7.22-7.09 (m, 3H), 3.89 (q, $J = 7.23$ Hz, 1H), 1.44 (d, $J = 7.20$ Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 200.4, 161.3 (d, $J = 245$ Hz), 130.0 (d, $J = 4.52$ Hz), 129.6 (d, $J = 8.37$ Hz), 125.9 (d, $J = 15.2$ Hz), 125.0 (d, $J = 3.47$ Hz), 116.0 (d, $J = 22.17$ Hz), 46.9, 13.8.

![2-(2-Fluoro-phenyl)-propionaldehyde](image)

**2-(2-Fluoro-phenyl)-propan-1-ol.** $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 7.30-7.18 (m, 2H), 7.15-7.12 (m, 1H), 7.10-7.00 (m, 1H), 3.72 (m, 2H), 3.28 (m, 1H), 1.45 (bs, 1H), 1.27 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 161.5 (d, $J = 244.3$ Hz), 131.2 (d, $J = 78.5$ Hz), 128.8 (d, $J = 5.1$ Hz), 128.2 (d, $J = 8.3$ Hz), 124.6 (d, $J = 3.5$ Hz), 115.7 (d, $J = 22.9$ Hz), 67.5, 35.9, 16.8.

Supelco’s Beta Dex 225, 95°C, 1mL/min, $t_{\text{major}} = 37.6$ min, $t_{\text{minor}} = 39.2$ min

![2-(2-Fluoro-phenyl)-propan-1-ol](image)

**2-(4-Chloro-phenyl)-propionaldehyde.** $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 9.65 (d, $J = 1.25$ Hz, 1H), 7.38-7.34 (m, 2H), 7.19-7.15 (m, 2H), 3.65 (q, $J = 7.12$ Hz, 1H), 1.42 (d, $J = 7.13$ Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 200.8, 136.9, 133.5, 130.1, 129.4, 52.5, 14.7.

![2-(4-Chloro-phenyl)-propionaldehyde](image)
2-(4-Chloro-phenyl)-propan-1-ol. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 7.32-7.28 (m, 2H), 7.21-7.18 (m, 2H), 3.65 (d, $J = 6.8$ Hz, 2H), 2.90 (m, 1H), 1.48 (bs, 1H), 1.24 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 143.1, 132.3, 129.3, 128.8, 68.6, 42.2, 17.7.

Supelco’s Beta Dex 225, 120$^\circ$C, 1mL/min, $t_{major} = 58.1$ min, $t_{minor} = 69.4$ min.

\[ \text{MeO} \quad \text{CHO} \]

2-(4-Methoxy-phenyl)-propionaldehyde. $^1$H NMR (360 MHz, CD$_2$Cl$_2$) $\delta$: 9.63 (d, $J = 1.41$ Hz, 1H), 7.15-7.11 (m, 2H), 6.93-6.89 (m, 2H), 3.79 (s, 3H), 3.58 (q, $J = 5.94$ Hz, 1H), 1.39 (d, $J = 7.09$ Hz, 3H); $^{13}$C NMR (90 MHz, CD$_2$Cl$_2$) $\delta$: 201.4, 159.4, 130.2, 129.7, 114.7, 55.6, 52.4, 14.8.

\[ \text{MeO} \quad \text{OH} \]

2-(4-Methoxy-phenyl)-propan-1-ol. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 7.18-7.13 (m, 2H), 6.88-6.83 (m, 2H), 3.77 (s, 3H), 3.62 (d, $J = 6.9$ Hz), 2.86 (m, 1H), 1.36 (bs, 1H), 1.22 (d, $J = 7.0$ Hz); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 158.7, 136.3, 128.7, 114.2, 69.0, 55.5, 42.0, 17.9.

Supelco’s Beta Dex 225, 130$^\circ$C, 1mL/min, $t_{major} = 34.6$ min, $t_{minor} = 36.2$ min.

\[ \text{MeO} \quad \text{CHO} \]

2-(4-Isobutyl-phenyl)-propionaldehyde. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 9.66 (d, $J = 1.41$ Hz, 1H), 7.19-7.11 (m, 4H), 3.61 (dq, $J = 7.1$, 1.2 Hz, 1H), 2.48 (d, $J = 7.2$}
Hz, 2H), 1.86 (M, 1H), 1.42 (d, \( J = 7.1 \) Hz, 3H), 0.91 (d, \( J = 6.6 \) Hz, 6H); \(^{13}\)C NMR (75 MHz, CD\(_2\)Cl\(_2\)) \( \delta \): 201.5, 141.4, 135.5, 130.1, 128.4, 126.3, 52.9, 45.2, 30.6, 22.4, 14.8.

2-(4-Isobutyl-phenyl)-propionic acid. \(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\)) \( \delta \): 11.8 (bs, 1H), 7.24-7.21 (m, 2H), 7.14-7.11 (m, 2H), 3.72 (q, \( J = 7.1 \) Hz, 1H), 2.46 (d, \( J = 7.1 \) Hz, 2H), 1.85 (m, 1H), 1.50 (d, \( J = 7.2 \) Hz, 3H), 0.91 (d, \( J = 6.6 \) Hz, 6H); \(^{13}\)C NMR (75 MHz, CD\(_2\)Cl\(_2\)) \( \delta \): 181.5, 141.3, 137.6, 129.7, 127.6, 45.3, 30.6, 22.5, 18.3.

Supelco’s Beta Dex 120, 180°C, 1mL/min, \( t_{\text{minor}} \) = 30.1 min, \( t_{\text{major}} \) = 31.2 min

NMR and Chiral GC Analysis of Hydroformylation Products of Vinyl Acetate Derivatives:

\[ \text{AcO} \quad \text{CHO} \]

**Propionic acid 1-methyl-2-oxo-ethyl ester**: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \): 9.54 (s, 1H), 5.08 (q, \( J = 7.19 \) Hz, 1H), 2.45 (dq, \( J = 5.96, 1.70 \) Hz, 2H), 1.40 (d, \( J = 7.20 \) Hz, 3H), 1.19 ppm (t, \( J = 7.57 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \): 198.6, 173.9, 74.4, 27.3, 14.1, 9.0 ppm.

Supelco’s Beta Dex 225, 100°C, 1mL/min, \( t_{\text{minor}} \) = 8.3 min, \( t_{\text{major}} \) = 9.0 min

\[ \text{AcO} \quad \text{CHO} \]

**Butyric acid 1-methyl-2-oxo-ethyl ester**: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \): 9.54, 5.08 (q, \( J = 7.16 \) Hz, 1H), 2.40 (t, \( J = 7.48 \) Hz, 2H), 1.70 (m, 2H), 1.39 (d, \( J = 7.18 \) Hz,
3H), 0.98 ppm (t, \( J = 7.41 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\) \( \delta \)): 198.6, 173.1, 74.4, 35.8, 18.4, 14.1, 13.6 ppm.

Supelco’s Beta Dex 225, 105°C, 1mL/min, \( t_{\text{minor}}(\text{minor}) = 9.4 \text{ min}, t_{\text{major}}(\text{major}) = 9.7 \text{ min}

\[ \text{Octanoic acid 1-methyl-2-oxo-ethyl ester: } \] \(^1\)H NMR (300 MHz, CDCl\(_3\) \( \delta \)): 9.54 (s, 1H), 5.08 (q, \( J = 7.19 \) Hz, 1H), 2.42 (dt, \( J = 7.49, 1.22 \) Hz, 2H), 1.67 (m, 2H), 1.40 (d, \( J = 7.19 \) Hz, 3H), 1.32-1.24 (m, 8H), 0.89 ppm (t, \( J = 7.01 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\) \( \delta \)): 198.6, 173.3, 74.4, 33.9, 31.6, 29.0, 28.9, 24.8, 22.6, 14.1, 14.0 ppm.

Supelco’s Beta Dex 225, 130°C, 1mL/min, \( t_{\text{minor}}(\text{minor}) = 20.1 \text{ min}, t_{\text{major}}(\text{major}) = 20.6 \text{ min}

\[ \text{Decanoic acid 1-methyl-2-oxo-ethyl ester: } \] \(^1\)H NMR (300 MHz, CDCl\(_3\) \( \delta \)): 9.51 (d, \( J = 0.50 \) Hz, 1H), 5.04 (q, \( J = 7.21 \) Hz, 1H), 2.39 (dq, \( J = 7.49, 1.25 \) Hz, 2H), 1.64 (m, 2H), 1.37 (d, \( J = 7.19 \) Hz, 3H), 1.31-1.24 (m, 12H), 0.85 ppm (t, \( J = 6.94 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\) \( \delta \)): 198.61, 173.26, 74.35, 33.93, 31.81, 29.36, 29.21, 29.04, 24.83, 22.63, 14.13, 14.07 ppm.

Supelco’s Beta Dex 225, 130°C, 1mL/min, \( t_{\text{minor}}(\text{minor}) = 54.7 \text{ min}, t_{\text{major}}(\text{major}) = 58.4 \text{ min}

\[ \text{2, 2-Dimethyl-propionic acid 1-methyl-2-oxo-ethyl ester: } \] \(^1\)H NMR (300 MHz, CDCl\(_3\) \( \delta \)): 9.52 (d, \( J = 0.59 \) Hz, 1H), 5.03 (dq, \( J = 7.17, 0.62 \) Hz, 1H), 1.40 (d, \( J = 7.17 \) Hz, 1H).
Hz, 3H), 1.27 ppm (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 198.7, 178.0, 74.3, 38.7, 27.1, 14.0 ppm.

Supelco’s Beta Dex 225, 100$^\circ$C, 1mL/min, $t_{(\text{minor})}$ = 41.6 min, $t_{(\text{major})}$ = 45.0 min

![Supelco’s Beta Dex 225](image)

**Benzoic acid 1-methyl-2-oxo-ethyl ester:** $^1$H NMR (300 MHz, CDCl$_3$) δ: 9.66 (d, $J = 0.63$ Hz, 1H), 8.11-8.08 (m, 2H), 7.63-7.57 (m, 1H), 7.49-7.44 (m, 2H), 5.30 (dq, $J = 7.16$, 0.60 Hz, 1H), 1.53 ppm (d, $J = 7.17$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 198.6, 165.9, 133.5, 129.8, 129.1, 128.5, 75.1, 14.3 ppm.

Supelco’s Beta Dex 225, 135$^\circ$C, 1mL/min, $t_{(\text{minor})}$ = 21.9 min, $t_{(\text{major})}$ = 24.3 min
References


(11) For figures of the space-filling and stick models (based on CAChe MM2 calculation) see ref. 10.


(18) This theoretical model does not take account of the chelation of the olefin functionality with the Rh center, which can also influence the enantioface selection during or prior to the insertion step somewhat. Meanwhile, we cannot rule out the possibility that both the steps of Rh-alkyl and Rh-acyl formation are reversible. In such situation, the enantioselectivity will be affected in the final product forming Rh-acyl hydrogenolysis step.


Chapter 3

Rh-Catalysed Asymmetric Hydroformylation of N-allylamides: A Highly Enantioselective Approach to $\beta^2$-Amino Aldehydes

3.1 Introduction

Asymmetric hydroformylation has attracted intensive attention since it can provide enantiomerically pure aldehydes atom-economically, which are important intermediates in the synthesis of a variety of pharmaceuticals and fine chemicals.\(^1\) Although a number of chiral phosphorus ligands have been developed for Rh-catalyzed asymmetric hydroformylation in the past decades,\(^2\) the substrates that have ever been hydroformylated with high enantioselectivities are still limited to simple functionalized terminal olefins without $\alpha$ hydrogens, such as styrene derivatives and vinyl carboxylates. It is highly desired to expand the substrate scope and popularize the application of this methodology.

Chiral $\beta^2$-amino aldehydes are important structural elements in a variety of pharmaceuticals and natural products.\(^3\) For instance, Boc ($\text{tert}$-butoxycarbonyl) protected amino aldehyde (3-(N-Boc-amino)-2-methylpropanol) is critical key building block in the synthesis of the Cyclamenol A (as shown in Scheme 3-1), which is known to inhibit adhesion of leukocytes to endothelial cells as new antiinflammatory agents.\(^4\) Its reduced product, 3-amino-2-methylpropanol, is start material for a number of 1$\beta$-
methylcarbapenem antibiotics, for example imipenem, panipenem and meropenem, which are currently in clinical use due to their broad antibacterial spectra and potent bactericidal effects. Its oxidized product, protected amino acid, is also important building block for a number of natural products such as Cryptophycins 1-4, which display considerable tumour-selective cytotoxicity both against multidrug-resistant tumour cell lines and solid tumours implanted in mice.

Scheme 3-1: Application of 3-(N-Boc-amino)-2-methylpropanol in Pharmaceutical and Synthetic Chemistry.
However, the previous synthesis of enantiomerically pure 3-(N-Boc-amino)-2-methylpropanol requires at least four steps, starting from expensive chiral source, hydroxyisobutyric acid with moderate yields (Scheme 3-2). The low efficiency prompted us to seek for an alternative approach to synthesize chiral β²-amino aldehydes. Since asymmetric hydroformylation can transform terminal olefins into chiral aldehydes, we envisioned that directly hydroformylation of N-allylamides can afford chiral β²-amino aldehydes much more efficiently and economically (Scheme 3-2).

Scheme 3-2: New Approach to Chiral β²-Amino Aldehydes. i) NH₃, MeOH, NaCN, 50°C; ii) BH₃·Me₂S, THF, reflux; iii) (Boc)₂O, Et₃N, MeOH; iv) (COCl)₂, DMSO, Et₃N.

Allylic compounds are particularly challenging substrates for rhodium-catalyzed asymmetric hydroformylation. It is well known that the double bonds of alkenes with α hydrogens can migrate into internal positions under hydroformylation conditions. In most cases, the linear aldehydes largely predominate over the branched ones in the product. For example, hydroformylation of allylbenzene derivatives and allylamines affords more linear isomers. Allylic alcohol have been hydroformylated into aldehyde in a branched-selective manner, base on the concept of substrate bound catalyst-directing phosphine groups. In particular, Breit and coworkers have completed tremendous work
in the regioselective hydroformylation of allylic alcohol derivatives with the ortho-
diphenylphosphanylbenzoate function. However, the tedious protecting and
deprotecting steps and the stoichiometric phosphine byproduct limited the application of
this method. In addition, optically pure aldehydes can only be obtained from chiral
substrates. N-allylamides have drawn much attention in hydroformylation as substrates, but the enantioselective version is seldom documented. Ojima and co-workers found that
the amide group can enhance selectivity for the isoaldehyde product in the
hydroformylation of N-allylamides which is ascribed to the chelation of the carbonyl
group to the rhodium center. This preference for branched products encouraged us to
use amide moieties as directing groups in the asymmetric hydroformylation reaction, instead of expensive and environmentally unfriendly phosphine groups.

Herein, we report a rhodium-catalyzed asymmetric hydroformylation reaction of
N-allylamides, N-allylsulfonamides, as well as other allylic substrates, with excellent
enantioselectivity (92 – 99% ee) and a turnover number (TON) of up to 9700; this
method provides an alternative, concise, and environmentally friendly route to chiral β2-
amino aldehydes, acids, and alcohols.

3.2 Results and Discussion

3.2.1 Optimization of Reaction Condition

We started our investigation using commercially available Boc-protected allyl
amine 1a as a model substrate, as facile removal of the Boc group affords the free β2-
amino aldehyde. We have previously reported that a class of hybrid phosphine-phosphoramidite ligands (yanphos A-C; Figure 3-1), are highly efficient in the asymmetric hydroformylation of styrene, vinyl acetate, and allyl cyanide.\textsuperscript{13} The high regio- and enantioselectivity afforded with these catalysts prompted us to consider them in the hydroformylation of \textit{1a}. Two other phosphoramidite ligands and several commercially available chiral ligands (Figure 3-1), which were highly efficient in the asymmetric hydroformylation of a variety of functionalized olefins, were also screened. The asymmetric hydroformylation reactions were carried out with 0.1 mol\% catalyst loading and 20 bar CO/H\textsubscript{2} (1:1) gas at 60 °C. The catalyst was prepared in situ by mixing [Rh(acac)(CO)\textsubscript{2}] with the ligand in toluene.
Some representative results are shown in Table 3-1. With (S,R)-yanphos derivatives as ligands, up to 93% ee, full conversion, and good regioselectivity were achieved (Table 3-1, entries 1-3). Other phosphoramidite ligands, (R)-monophos (E) and (R)-triphosorus ligand F, were also investigated but afforded no more than 50% ee (Table 3-1, entries 5 and 6). (S,R)-Binaphos provided the product in 78% ee, but gave less of the desired branched product than the linear one (Table 3-1, entry 4). Hydroformylation with (S,S)-BDPP [(2S,4S)-2,4-Bis(diphenylphosphino)pentane] and (S,S)-Ph-BPE [(+)-1,2-Bis((2S,5S)-2,5-diphenylphospholano)ethane] offered good
regioselectivity (83:17 and 86:14, respectively), whilst the enantioselectivity were less satisfying (Table 3-1, entries 7 and 8). It is worth to note that, under current reaction conditions, all of the linear aldehyde 3a was transformed into 2-hydroxy pyrrolidine 4a in quantitative yield, by intramolecular attack of the primary amide on the carbonyl group (as shown in Table 3-1).\textsuperscript{15}

Table 3-1: Ligand Screening for Asymmetric Hydroformylation of N-allylamide 1a.\textsuperscript{a}

<table>
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<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conversion [%]\textsuperscript{b}</th>
<th>b/l\textsuperscript{b}</th>
<th>ee [%]\textsuperscript{c}</th>
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<td>1</td>
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<td>B</td>
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<td>C</td>
<td>98</td>
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<tr>
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<td>D</td>
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<td>E</td>
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<tr>
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<td>G</td>
<td>43</td>
<td>83/17</td>
<td>56(R)</td>
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<td>8</td>
<td>H</td>
<td>93</td>
<td>86/14</td>
<td>87(R)</td>
</tr>
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Reactions were performed on a 1.0 mmol scale at 60 °C in toluene with substrate/Rh=1000, L:Rh=4:1, 20 bar 1:1 CO/H₂, and a reaction time of 20 h. Determined by ¹H NMR, b/l (branched/linear ratio) = 2a/4a. Determined by chiral GC analysis. The absolute configuration was assigned by comparing the sign of the optical rotation of the reduced product, tert-butyl (3-hydroxy-2-methylpropyl)carbamate, with literature.

The success of ligand B encouraged us to investigate the effects of solvent, syngas pressure, and reaction temperature to obtain optimal conditions. Obvious solvent dependency was observed in the asymmetric hydroformylation reactions catalyzed by rhodium-B complexes (Table 3-2, entries 1-5). Nonpolar solvent provided better activity and selectivity than polar solvent. Of the solvents tested, toluene gave the best conversion, regio- and enantioselectivity. A decrease of the pressure from 20 to 10 bar resulted in a slight increase of the regio- and enantioselectivity, and the inverse was also observed (Table 3-2, entries 6 and 7). Lowering the temperature from 60 °C to 40 °C led to a slight increase in ee value, but a dramatic decrease in conversion. Likewise, a higher temperature lowered the enantioselectivity (Table 3-2, entries 8 and 9).

Table 3-2: Asymmetric Hydroformylation of N-allylamide 1a under Different Reaction Conditions.

\[
\begin{align*}
\text{BocHN} & \xrightarrow{\text{Rh(acac)(CO)₂/B}} \text{BocHN} & \xrightarrow{\text{CO/H₂}} \text{BocHN} \\
1a & \quad \text{CHO} & \quad \text{BocN} \\
\text{2a} & \quad \text{HO} & \quad \text{4a}
\end{align*}
\]
<table>
<thead>
<tr>
<th>Entry</th>
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<th>CO/H₂ [bar]</th>
<th>T [°C]</th>
<th>Conv. [%]ᵇ</th>
<th>b/lᵇ</th>
<th>ee [%]ᶜ</th>
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ᵇ Reactions were performed on a 1.0 mmol scale with substrate/Rh=1000, B:Rh=4:1, and a reaction time of 20 h. ᵇ Determined by ¹H NMR, b/l (branched/linear ratio) = 2a/4a. ᵇ See footnote of Table 3-1.

3.2.2 Asymmetric Hydroformylation of N-Allylamide with Ligand B

With the optimized reaction conditions in hand (Table 3-3, entry 6), we examined the scope of the methodology with regards to functional group tolerance. Using a rhodium-B catalyst, a variety of N-allylamides, N-allylsulfonamides, and N-allylphthalimide were hydroformylated with complete conversion, good regioselectivity, and excellent enantioselectivity (> 92 % ee). The functionality on the amide had no significant effect on the enantioselectivity, but slightly influenced the regioselectivity.
(Table 3-3, entries 1-3). For the sulfonamide substrates, the electronic properties of the substituents at the para position of the phenyl group had a marked effect on the branched/linear selectivity. Electron-rich groups increased the enantioselectivity (Table 3-3, entries 3-5), whilst introducing a methyl group onto the nitrogen atom of 1e did not affect the hydroformylation reaction (Table 3-3, entries 6). However, substrates that contained N,N-bis(carbonyl) groups showed much better regio- and enantioselectivities. N-allylphthalimide afforded 96 % ee and a branched/linear ratio of 84:16 (Table 3-3, entry 7). Notably, 99 % ee was achieved in the hydroformylation of N,N-bis(Boc)-N-allylamine (Table 3-3, entry 8). To further investigate the reactivity of rhodium-B system in the hydroformylation of N-allylamides, a reaction was carried out on a 10.0 mmol scale with substrate/Rh=10000:1 for 24 hours; 97 % conversion (TON = 9700) was achieved without sacrificing the regio- and enantioselectivity (Table 3-3, entry 9). N-Boc-protected β3-amino aldehyde 2a was obtained by flash chromatography in 62 % yield.
Table 3-3: Asymmetric Hydroformylation of \( N \)-Allylamides 1.

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 & \quad \text{Conv. [%]}^b & \quad \text{b/l}^b & \quad \text{ee [%]}^c \\
1 & \text{Boc (1a)} & \text{H} & >99 & 66/34 & 94 \\
2 & \text{Bz (1b)} & \text{H} & >99 & 78/22 & 95 \\
3 & \text{Ts (1c)} & \text{H} & >99 & 67/33 & 94 \\
4 & \text{p-NO}_2\text{PhSO}_2 \text{(1d)} & \text{H} & >99 & 72/28 & 92 \\
5 & \text{p-MeOPhSO}_2 \text{(1e)} & \text{H} & >99 & 71/29 & 96 \\
6 & \text{Ts (1f)} & \text{Me} & >99 & 67/33 & 94 \\
7 & \text{Phthaloyl (1g)} & & >99 & 84/16 & 96 \\
8 & \text{Boc (1h)} & \text{Boc} & >99 & 72/28 & 99 \\
9^d & \text{Boc (1a)} & \text{H} & 97 & 66/34 & 94
\end{align*}
\]

\(^a\) Reactions were performed on a 1.0 mmol scale at 60 °C in toluene with substrate/Rh=1000, \( \text{B:Rh}=4:1 \), 10 bar 1:1 \( \text{CO}/\text{H}_2 \) and a reaction time of 20 h. When \( \text{R}^2 = \text{H} \), the linear product 3a-e transformed to 2-hydroxy pyrrolidines in quantitative yield. \(^b\) Determined by \(^1\text{H} \) NMR spectroscopy. \(^c\) Determined by chiral GC or chiral HPLC analysis, see supporting information for experimental details. \(^d\) Reaction were performed on a 10.0 mmol scale with substrate/Rh=10000 for 24h.
The further transformation of $\beta^2$-amino aldehyde 2a into the corresponding acid and alcohol was proved to be straightforward and practical. 2a was treated with NaClO$_2$, 2-methyl-2-butene in sodium dihydrogen phosphate to afford $\beta^2$-amino acid 9 in high yield and without sacrificing the ee values (96 % yield, 94 % ee). $\beta^2$-Amino acid 9 is an important building block for a number of natural products, such as cryptophycins 1-4. Reduction of aldehyde 2a with sodium borohydride gave $\beta^2$-amino alcohol 10 (95 % yield, 94 % ee), a starting material for 1β-methylcarbapenem antibiotics (Scheme 3-3).

Scheme 3-3: Synthesis of $\beta^2$-Amino Acid and Alcohol.

3.2.3 Asymmetric Hydroformylation of Other Allylic Compounds with Ligand B

To further explore the application of this methodology, several other functionalized allylic substrates were employed in the rhodium-B-catalyzed asymmetric hydroformylation reaction (Scheme 3-4). The results showed that the functional group on the substrate has no obvious effect on the enantioselectivity, but influenced the branch/linear product ratio very much. Allyl phenyl ether 5 and allyltrimethylsilane 7 gave comparable results to $N$-allylamide substrates. Allyl acetate 6 and allylbenzene 8
both afforded high enantioselectivity (94%), but linear aldehydes predominated in the product.

Scheme 3-4: Asymmetric Hydroformylation of Functional Allyl Substrates.

3.3 Conclusion

In conclusion, a variety of allylic substrates have been successfully employed in a rhodium-yanhos-catalyzed hydroformylation reaction under mild conditions, with up to 99 % ee and 9700 TON. To the best of our knowledge, this is the first example of applying N-allylamides and N-allylsulfonamides in asymmetric hydroformylation. This reaction provides an alternative catalytic route to $\beta^2$-amino aldehydes, acids, and alcohols, which have promising application in pharmaceutical and synthetic chemistry. Further studies to improve the regio- and enantioselectivity and to explore more applications of this catalyst are underway.
**Experimental Section**

**General Methods:** All reactions and manipulations that were sensitive to moisture or air were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. Solvents were dried with standard procedures and degassed with N₂. Column chromatography was performed using 200-400 mesh silica gel supplied by Natland International Corp. Thin-layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. ¹H, ¹³C, and ³¹P NMR spectra were recorded in CDCl₃ or CD₂Cl₂ on Bruker Avance 400 MHz spectrometers or Varian Mercury 500 MHz FT-NMR spectrometer. Optical rotation was obtained on a Perkin-Elmer 341 MC polarimeter. HRMS were recorded on a Thermo LTQ Orbitrap hybrid mass spectrometer. GC analysis was carried out on Hewlett-Packard 7890 gas chromatography using chiral capillary columns. HPLC analysis was carried out on Agilent 1200 series. Compound 1a is commercially available from Sigma-Aldrich company.

**General Procedure for The Preparation of N-Allylamides:**

To a solution of benzoyl chloride (2.40 mL, 20.7 mmol) in CH₂Cl₂ (80 mL) was added dropwise a solution of allylamine (1.52 mL, 20.0 mmol) and Et₃N (2.90 mL, 20.7 mmol) in CH₂Cl₂ (20 mL) at 0 °C. After the addition, the reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (50 mL) and the aqueous layer was washed with CH₂Cl₂ (50 mL). The organic layers were combined and evaporated under vacuum. The residue was subjected to column chromatography on silica-gel to afford 1b.
**N-allylbenzamide (1b):** yield = 95%; colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.72 (d, $J = 8.0$ Hz, 2H), 7.41-7.37 (m, 1H), 7.32-7.29 (m, 2H), 6.67 (br, 1H), 5.82 (ddt, $J = 17.2$, 10.4, 5.6 Hz, 1H), 5.14 (dq, $J = 17.2$, 1.6 Hz, 1H), 5.06 (dq, $J = 10.4$, 1.6 Hz, 1H), 3.98-3.94 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 167.5, 134.5, 134.2, 131.4, 128.5, 127.0, 116.5, 42.4 ppm.

**N-allyl-4-methylbenzenesulfonamide (1c):** yield = 92%; white solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.67 (d, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 2H), 5.60 (ddt, $J = 17.2$, 10.4, 7.0 Hz, 1H), 5.27 (t, $J = 7.0$ Hz, 1H), 5.05 (dq, $J = 17.2$, 1.6 Hz, 1H), 4.94 (dq, $J = 10.4$, 1.2 Hz, 1H), 3.45 (tt, $J = 7.0$, 1.6 Hz, 2H), 2.30 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 143.4, 137.0, 133.1, 129.7, 127.2, 117.4, 45.7, 21.5 ppm.

**N-allyl-4-nitrobenzenesulfonamide (1d):** yield = 99%; pale yellow solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.37 (dt, $J = 8.8$, 2.0 Hz, 2H), 8.06 (dt, $J = 9.2$, 2.0 Hz, 2H), 5.72 (ddt, $J = 17.2$, 10.4, 7.0 Hz, 1H), 5.18 (dq, $J = 17.2$, 1.2 Hz, 1H), 5.14 (dq, $J = 10.4$, 0.9 Hz, 1H), 4.72 (t, $J = 4.8$ Hz, 1H), 3.70 (tt, $J = 7.0$, 1.6 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 150.2, 146.2, 132.4, 128.4, 124.4, 118.4 45.9 ppm.
N-allyl-4-methoxybenzenesulfonamide (1e): yield = 96 %; pale yellow solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.71 (d, $J = 9.2$ Hz, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 5.60 (ddt, $J = 17.2$, 10.0, 7.0 Hz, 1H), 5.30 (t, $J = 7.0$ Hz, 2H), 5.24 (dd, $J = 17.2$, 1.2 Hz, 1H), 4.94 (dq, $J = 10.0$, 1.2 Hz, 1H), 3.74 (s, 3H), 3.44 (t, $J = 7.0$, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 162.9, 133.2, 131.5, 129.2, 117.4, 114.3, 55.7, 45.7 ppm.

N-allyl-N-methyl-4-methylbenzenesulfonamide (1f): $^{16}$

N-allyl-4-methylbenzenesulfonamide 1c (2.11 g, 10.0 mmol) was added in portions to a suspension of sodium hydride (0.53 g, 22.0 mmol) in anhydrous THF at 0 °C and stirred for 1 h at room temperature. Then methyl iodide (12.45 mL, 200.0 mmol) was added to this solution at 0 °C. The mixture was refluxed overnight. Water was added and THF was removed under vacuum. The product was extracted with ethyl acetate. The extracts were dried over sodium sulfate, the solvents were removed, and the residue was subjected to column chromatography on silica-gel with ethylacetate-hexane mixture (5:1) to afford 1f (yield = 99 %) as pale yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.68 (d, $J = 8.4$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 5.60 (ddt, $J = 17.2$, 10.0, 9.6 Hz, 1H), 5.20 (dt, $J = 3.2$, 1.6 Hz, 1H), 5.17 (dd, $J = 2.8$, 1.6 Hz, 1H), 3.62 (d, $J = 6.4$ Hz, 2H), 2.66 (s, 3H), 2.44 (s, 3H), 3.44 (t, $J = 7.0$, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 143.4, 134.6, 132.7, 129.7, 127.5, 119.1, 53.1, 34.2, 21.5 ppm.
**N-allylphthalimide (1g):** To a suspension of 10.2 g (54 mmol) potassium phthalimide (9.46 g, 50.0 mmol) and tetrabutylammoniumbromide (0.32 g, 1.0 mmol) in 50 ml anhydrous DMF was added allylbromide (4.37 mL, 50.0 mmol) dropwise. The mixture is stirred at room temperature over night and then poured into 50 ml water. The solid is filtrated and washed with water. The crude product is purified by recrystallization from hexane to yield 1g (yield = 80 %) as white crystal; $^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.86 (ddd, $J$ = 6.4, 4.4, 1.2 Hz, 2H), 7.72 (ddd, $J$ = 6.4, 4.4, 1.2 Hz, 2H), 5.89 (ddt, $J$ = 17.2, 10.4, 5.6 Hz, 1H), 5.25 (dt, $J$ = 17.2, 1.2 Hz, 1H), 5.20 (dt, $J$ = 10.4, 1.2 Hz, 1H), 4.30 (dq, $J$ = 5.6, 1.2 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 167.9, 134.0, 132.2, 131.6, 123.3, 117.8, 40.1 ppm.

**N,N-Bis(tert-butoxycarbonyl)allylamine (1h):** To a 100 mL flask were charged di-tert-butylinimidicarboxylate (2.0 g, 9.2 mmol), allyl bromide (0.97 mL, 11.0 mmol), terabutylammonium bromide (0.44 g, 0.14 mmol), NaOH (50% w/w, 4 mL, 46 mmol), water (10 mL), and 2-Methyl-THF (10 mL), and the mixture was heated to 42 °C for 2 h with stirring. The product was extracted with ethyl acetate. The extracts were dried over sodium sulfate, the solvents were removed, and the residue was subjected to column chromatography on silica-gel with ethylacetate-hexane mixture (5:1) to afford 1h (yield = 95 %) as colorless oil; $^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$: 5.89 (ddt, $J$ = 17.2, 10.0, 6.4 Hz, 1H), 5.16 (dd, $J$ = 17.2, 1.6 Hz, 1H), 5.20 (dt, $J$ = 10.0, 1.6 Hz, 1H), 4.17
(dq,  J = 6.4, 1.2 Hz, 2H), 1.50 (s, 18H); 13C NMR (100 MHz, CDCl₃) δ: 152.3, 133.8, 116.2, 82.3, 48.5, 28.0 ppm.

**General Procedure for Asymmetric Hydroformylation:**

In a glovebox filled with nitrogen, to a 2 mL vial equipped with a magnetic bar was added ligand B (0.004 mmol) and Rh(acac)(CO)₂ (0.001 mmol in 0.20 mL solvent). After stirring for 10 min, substrate (1.0 mmol) and additional solvent was charged to bring the total volume of the reaction mixture to 1.0 mL. The vial was transferred into an autoclave and taken out of the glovebox. Carbon monoxide (5 atm) and hydrogen (5 atm) were charged in sequence. The reaction mixture was stirred at 60 °C (oil bath) for 20 h. The reaction was cooled and the pressure was carefully released in a well ventilated hood. The conversion and branch/linear ratio were determined by ¹H NMR spectroscopy from the crude reaction mixture. The enantiomeric excesses of 2a and products of 5-8 were determined by chiral GC analysis with a Supelco’s Beta Dex 225 column from the crude reaction mixture. The ee of 2b-2f and 2h were determined by reducing them to alcohol with NaBH₄ and analyzing with HPLC under condition in the following. The ee of 2g by oxidizing it into acid with Jone’s reagent and then reacting with TMSCH₂N₂ to afford the corresponding ester which was analyzed with HPLC.

**Hydroformylation of Styrene at High Substrate/Catalyst Ratio:**

In a glovebox filled with nitrogen, to a 20 mL vial equipped with a magnetic bar was added ligand B (0.004 mmol) and Rh(acac)(CO)₂ (0.001 mmol in 0.10 mL solvent). After stirring for 10 min, substrate (10.0 mmol) and additional solvent was charged to
bring the total volume of the reaction mixture to 10.0 mL. The vial was transferred into an autoclave and taken out of the glovebox. Carbon monoxide (5 atm) and hydrogen (5 atm) were charged in sequence. The reaction mixture was stirred at 60 °C (oil bath) for 20 h. The reaction was cooled and the pressure was carefully released in a well ventilated hood. The conversion, branch/linear ratio and enantiomeric excesses of 2a were determined in the same method as above.

**Determine the Enantiomeric Excess of Product 2g:**

A portion of the reaction mixture (about 1/10) was diluted with acetone (10 mL) and 1 ml of Jones reagent was added dropwise in a ice bath. The solution was allowed to stir at room temperature for 1 h. To the resulting green mixture was added water (10 mL). The resulting mixture was stirred for 5 min and extracted with CH₂Cl₂ (10 mL). The combined organic layer was dried over Na₂SO₄ and concentrated. The residue was dissolved in a mixture of THF/Methanol (2 mL, v/v 2:1). To this solution, (trimethylsilyl)diazomethane solution (0.2 mL, 2.0 M in diethyl ether) was added in a ice bath under nitrogen atmosphere. The mixture was allowed to stir at room temperature for 30 min, then was concentrated under reduced pressure. The residue was subjected a flash chromatography on silica gel (elution with Hexane/EtOAc 3:1). The obtained ester was analyzed by Chiral GC (Supelco β-120) to determine the enantiomeric excess.
Characterization Data (Optical Rotation, NMR and GC/HPLC condition) of Hydroformylation Products and Their Derivatives

(S)-tert-butyl (2-methyl-3-oxopropyl)carbamate (2a): \([\alpha]^{24}_{D} = -26.5 \text{ (c = 1.5, CHCl}_3\) at 94% ee; Enantiomeric excess was determined by GC with a Supelco’s Beta Dex 225 column, Temperature program: 120 °C, 1 °C/min to 150 °C, stay 10 mins, Flow rate = 1.0 mL/min, \(t_{\text{minor}} = 20.9\) min, \(t_{\text{major}} = 21.1\) min; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 9.64 (s, 1H), 4.99 (m, 1H), 3.28 (d, \(J = 6.4\) Hz, 2H), 2.56-2.61 (m, 1H), 1.31 (s, 9H), 1.11 (d, \(J = 7.2\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 203.9, 155.9, 79.4, 47.2, 40.6, 28.3, 11.2 ppm; HRMS (ESI): \(m/z\): calcd for \(\text{C}_9\text{H}_{18}\text{NO}_3\) ([M+H]+): 188.1287; found: 188.1281.

 tert-butyl 2-hydroxypyrrolidine-1-carboxylate (4a): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 9.64 (s, 1H), 4.99 (m, 1H), 3.28 (d, \(J = 6.4\) Hz, 2H), 2.56-2.61 (m, 1H), 1.31 (s, 9H), 1.11 (d, \(J = 7.2\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 203.9, 155.9, 79.4, 47.2, 40.6, 28.3, 11.2 ppm.

\(N\)-(3-hydroxy-2-methylpropyl)benzamide (Table 3, entry 2): \([\alpha]^{24}_{D} = 15.1^\circ \text{ (c = 1.0, CHCl}_3\) at 95% ee; Enantiomeric excess was determined by HPLC analysis: Daicel Chiralcel OD-H, hexane/iPrOH = 95:5, flow rate = 1.0 mL/min, \(\lambda\)
= 254 nm, t_{minor} = 27.2 min, t_{major} = 30.2 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.77 (d, $J$ = 7.2 Hz, 2H), 7.49 (t, $J$ = 7.2 Hz, 1H), 7.40 (t, $J$ = 7.6 Hz, 2H), 7.13 (br, 1H), 3.86 (br, 1H), 3.65-3.59 (m, 2H), 3.40-3.29 m, 2H), 1.95-1.86 (m, 1H), 0.93 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 168.8, 134.2, 131.6, 128.6, 127.0, 65.2, 43.1, 35.9, 14.7 ppm; HRMS (ESI): $m/z$: calcd for C$_{11}$H$_{16}$NO$_2$ ([M+H]$^+$): 194.1181; found: 194.1174.

$N$-(4-hydroxybutyl)benzamide (Table 3, entry 2):

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.75 (d, $J$ = 8.0 Hz, 2H), 7.45 (t, $J$ = 7.0 Hz, 1H), 7.37 (t, $J$ = 7.5 Hz, 2H), 6.93 (br, 1H), 3.66 (t, $J$ = 6.0 Hz, 2H), 3.44 (m, 1H), 2.87 (br, 1H), 1.65 (tt, $J$ = 6.0, 6.5 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 167.9, 134.6, 131.4, 128.5, 126.9, 62.2, 39.9, 29.8, 26.2 ppm.

$N$-(3-hydroxy-2-methylpropyl)-4-methylbenzenesulfonamide (Table 3, entry 3): $\left[\alpha\right]_{24}^D = 5.3$ (c = 2.0, CHCl$_3$) at 94% ee; Enantiomeric excess was determined by HPLC analysis: Daicel Chiralcel AD, hexane/iPrOH = 85:15, flow rate = 1.0 mL/min, $\lambda = 205$ nm, t_{major} = 14.0 min, t_{minor} = 19.4 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.75 (d, $J$ = 8.0 Hz, 2H), 7.31 (d, $J$ = 8.0 Hz, 2H), 5.50 (t, $J$ = 6.4 Hz, 1H), 3.67-3.63 (m, 1H), 3.49-3.44 (m, 1H), 3.01-2.94 (m, 1H), 2.91-2.84 (m, 1H), 2.50 (br, 1H), 2.43 (s, 3H), 1.90-1.80 (m, 1H), 0.85 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 143.2, 136.9, 129.6, 126.9, 65.4, 46.5, 35.3, 21.4,
14.3 ppm; HRMS (ESI): \( m/z \): calcd for \( \text{C}_{11}\text{H}_{18}\text{NO}_{3}\text{S} \) ([M+H]\(^+\)): 244.1007; found: 244.1007.

\( N-(4\text{-hydroxybutyl})-4\text{-methylbenzenesulfonamide} \) (Table 3, entry 3): \(^1\text{H NMR} \) (500 MHz, CDCl\(_3\)) \( \delta \): 7.74 (d, \( J = 8.0 \text{ Hz}, 2\text{H} \)), 7.30 (d, \( J = 8.0 \text{ Hz}, 2\text{H} \)), 3.60 (t, \( J = 6.0 \text{ Hz}, 2\text{H} \)), 2.95 (t, \( J = 6.5 \text{ Hz}, 2\text{H} \)), 2.42 (s, 3H), 1.56 (tt, \( J = 6.5, 6.0 \text{ Hz}, 4\text{H} \)); \(^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)) \( \delta \): 143.3, 136.9, 129.7, 127.1, 62.2, 43.0, 29.5, 26.3, 21.5 ppm.

\( N-(3\text{-hydroxy-2-methylpropyl})-4\text{-nitrobenzenesulfonamide} \) (Table 3, entry 4): \([\alpha]^{24}_D = 5.6 \) (c = 1.0, CHCl\(_3\)) at 92\% ee; Enantiomeric excess was determined by HPLC analysis: Daicel Chiralcel AD, hexane/iPrOH = 85:15, flow rate = 1.0 mL/min, \( \lambda = 254 \text{ nm} \), \( t_{\text{major}} = 32.4 \text{ min} \), \( t_{\text{minor}} = 40.1 \text{ min} \); \(^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \): 8.37 (d, \( J = 8.8 \text{ Hz}, 2\text{H} \)), 8.06 (d, \( J = 8.0 \text{ Hz}, 1\text{H} \)), 5.65 (br, 1H), 3.74-3.70 (m, 1H), 3.50-3.45 (m, 1H), 3.14-3.08 (m, 1H), 2.99-2.93 (m, 1H), 2.01 (br, 1H), 1.96-1.85 (m, 1H), 0.88 (d, \( J = 7.2 \text{ Hz}, 3\text{H} \)); \(^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)) \( \delta \): 150.1, 146.1, 128.3, 124.4, 66.7, 47.6, 35.0, 14.3 ppm; HRMS (ESI): \( m/z \): calcd for \( \text{C}_{10}\text{H}_{15}\text{N}_{2}\text{O}_{5}\text{S} \) ([M+H]\(^+\)): 275.0702; found: 275.0697.
N-(4-hydroxybutyl)-4-nitrobenzenesulfonamide (Table 3, entry 4): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.36 (d, $J = 7.5$ Hz, 2H), 8.05 (d, $J = 7.5$ Hz, 2H), 5.47 (br, 1H), 3.66 (t, $J = 6.0$ Hz, 2H), 3.05 (t, $J = 6.5$ Hz, 2H), 1.73 (br, 1H), 1.61 (tt, $J = 6.5$, 6.0 Hz, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 150.0, 146.2, 128.3, 124.4, 62.3, 43.3, 29.4, 26.7 ppm.

N-(3-hydroxy-2-methylpropyl)-4-methoxybenzenesulfonamide (Table 3, entry 5): $\left[\alpha\right]_{D}^{24} = 3.6$ (c = 2.0, CHCl$_3$) at 96% $ee$; Enantiomeric excess was determined by HPLC analysis: Daicel Chiralcel AD, hexane/iPrOH = 85:15, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_{major}$ = 20.7 min, $t_{minor}$ = 28.6 min; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.78 (dd, $J = 9.0$, 1.5 Hz, 2H), 6.96 (dd, $J = 9.0$, 1.5 Hz, 2H), 3.85 (s, 3H), 3.64-3.61 (m, 1H), 3.47-3.43 (m, 1H), 2.96-2.92 (m, 1H), 2.87-2.83 (m, 1H), 1.86-1.79 (m, 1H), 0.83 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 162.9, 131.5, 129.1, 114.3, 65.9, 55.6, 46.7, 35.3, 14.4 ppm; HRMS (ESI): $m/z$: calcd for C$_{11}$H$_{18}$NO$_4$S ([M+H]+): 260.0957; found: 260.0954.

N-(4-hydroxybutyl)-4-methoxybenzenesulfonamide (Table 3, entry 5): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.79 (d, $J = 9.0$ Hz, 2H), 6.97 (d, $J = 9.0$ Hz, 2H), 3.87 (s, 3H), 3.62 (t, $J = 6.0$ Hz, 2H), 2.96
(t, \( J = 6.5 \) Hz, 2H), 1.57 (tt, \( J = 6.5, 6.0 \) Hz, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 162.9, 131.6, 129.2, 114.3, 62.2, 55.6, 43.0, 29.6, 26.3 ppm.

\[ \text{N-(3-hydroxy-2-methylpropyl)-N-Methyl-4-methylbenzenesulfonamide (Table 3, entry 6): } \]

\[ [\alpha]^{24}_D = -13.6 \text{ (c = 2.0, CHCl}_3\text{) at 94\% ee}; \] Enantiomeric excess was determined by HPLC analysis: Daicel Chiralcel AS, hexane/iPrOH = 94:6, flow rate = 1.0 mL/min, \( \lambda = 205 \text{ nm, } t_{\text{minor}} = 32.6 \text{ min, } t_{\text{major}} = 36.5 \text{ min}; \]
\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 7.57 (d, \( J = 8.0 \) Hz, 2H), 7.24 (d, \( J = 8.0 \) Hz, 2H), 3.61 (dd, \( J = 11.0, 4.5 \) Hz, 1H), 3.43 (dd, \( J = 11.0, 5.0 \) Hz, 1H), 3.00 (dd, \( J = 13.5, 8.0 \) Hz, 1H), 2.65 (s, 3H), 2.91-2.84 (dd, \( J = 14.5, 8.0 \) Hz, 1H), 2.34 (s, 3H), 1.85-1.79 (m, 1H), 0.87 (d, \( J = 7.0 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 143.5, 134.0, 129.7, 127.3, 64.3, 53.0, 35.7, 34.0, 21.4, 14.5 ppm; HRMS (ESI): \( m/z \): calcd for C\(_{12}\)H\(_{20}\)NO\(_3\)S ([M+H]\(^+\)): 258.1164; found: 258.1161.

\[ \text{N-(4-hydroxybutyl)-N-Methyl-4-methylbenzenesulfonamide (Table 3, entry 6): } \]

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 7.64 (d, \( J = 8.0 \) Hz, 2H), 7.30 (d, \( J = 7.5 \) Hz, 2H), 3.66 (t, \( J = 5.5 \) Hz, 2H), 3.01 (t, \( J = 6.5 \) Hz, 2H), 2.69 (s, 3H), 2.41 (s, 3H), 1.88 (br, 1H), 1.61 (tt, \( J = 6.5, 5.5 \) Hz, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 143.3, 134.5, 129.7, 127.4, 62.3, 49.9, 34.6, 29.4, 24.0, 21.5 ppm.
Methyl 2-(phthalimidomethyl)-propanoate (Table 3, entry 7): \([\alpha]^{24}_D = 18.7 \text{ (c = 1.0, CHCl}_3\text{) at 96\% ee}; (R): \text{lit.}[19] \ [\alpha]^{25}_D = -17.2 \text{ (c = 0.95, CHCl}_3\text{) for 84\% ee}; \text{Enantiomeric excess was determined by HPLC analysis: Daicel Chiralcel OD-H, hexane/iPrOH = 90:10, flow rate = 0.5 mL/min, } \lambda = 254 \text{ nm, } t_{\text{minor}} = 19.6 \text{ min, } t_{\text{major}} = 21.9 \text{ min}; ^1\text{H NMR (500 MHz, CDCl}_3\text{)} \delta: 7.79 (dd, J = 5.5, 3.0 Hz, 2H), 7.68 (dd, J = 5.5, 3.0 Hz, 2H), 3.92 (dd, J = 14.0, 7.5 Hz, 1H), 3.73 (dd, J = 14.0, 7.0 Hz, 1H), 3.62 (s, 3H), 2.97-2.90 (m, 1H), 1.16 (d, J = 7.0 Hz, 3H); ^13\text{C NMR (100 MHz, CDCl}_3\text{)} \delta: 174.3, 168.1, 134.0, 131.9, 123.3, 52.0, 40.5, 38.5, 14.6 ppm.

\[ \text{N,N-Bis(tert-butoxycarbonyl)-3-hydroxy-2-methylpropylamine (Table 3, entry 8): } [\alpha]^{24}_D = -9.5 \text{ (c = 1.0, CHCl}_3\text{) at 99\% ee}; \text{Enantiomeric excess was determined by HPLC analysis: Daicel Chiralcel AD, hexane/iPrOH = 95:5, flow rate = 0.5 mL/min, } \lambda = 205 \text{ nm, } t_{\text{minor}} = 9.9 \text{ min, } t_{\text{major}} = 12.5 \text{ min}; ^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta: 3.63-3.29 (m, 4H), 1.86-1.78 (m, 1H), 1.44 (s, 18H), 0.88 (d, J = 7.2 Hz, 3H); ^13\text{C NMR (100 MHz, CDCl}_3\text{)} \delta: 152.8, 82.2, 62.5, 46.0, 29.7, 28.1, 25.4 ppm; \text{HRMS (ESI): } m/z: \text{caled for C}_{14}\text{H}_{28}\text{NO}_5 ([M+H]^+) = 290.1967; \text{found: 290.1968.} \]
2-methyl-3-phenoxypropanal (product of 5): Enantiomeric excess was determined by GC with a Supelco’s Beta Dex 225 column, Temperature program: 90 °C, 1 °C/min to 160 °C, Flow rate = 1.0 mL/min, \( t_{\text{minor}} = 44.3 \) min, \( t_{\text{major}} = 44.5 \) min; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 9.80 (s, 1H), 7.31-7.25 (m, 2H), 6.98-6.94 (m, 1H), 6.94-6.87 (m, 2H), 4.22-4.18 (m, 1H), 4.15-4.12 (m, 1H), 2.89-2.81 (m, 1H), 1.26 (d, \( J = 7.2 \) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 202.9, 158.6, 129.5, 121.2, 114.6, 67.7, 46.3, 10.8 ppm.

4-phenoxybutanal (product of 5): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 9.87 (s, 1H), 7.31-7.25 (m, 2H), 6.98-6.94 (m, 1H), 6.94-6.87 (m, 2H), 4.00 (t, \( J = 6.0 \) Hz, 2H), 2.66 (t, \( J = 7.2 \) Hz, 2H), 2.12 (tt, \( J = 7.2, 6.0 \) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 158.7, 129.5, 120.9, 114.5, 66.6, 40.7, 22.1 ppm.

2-methyl-3-oxopropyl acetate (product of 6): Enantiomeric excess was determined by GC with a Supelco’s Beta Dex 225 column, Temperature program: 90 °C, 1 °C/min to 108 °C, 4 °C/min to 132 °C, Flow rate = 1.0 mL/min, \( t_{\text{minor}} = 16.7 \) min, \( t_{\text{major}} = 17.0 \) min; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 9.70 (s, 1H), 4.33-4.25 (m, 2H), 2.76-2.66 (m, 1H), 1.17 (d, \( J = 7.2 \) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 202.0, 170.8, 63.7, 45.7, 20.7, 10.6 ppm.
4-oxobutyl acetate (product of 6): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 9.80 (s, 1H), 4.10 (t, $J = 6.0$ Hz, 2H), 2.55 (t, $J = 7.2$ Hz, 2H), 2.05 (s, 3H), 1.98 (tt, $J = 7.2, 6.0$ Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 201.1, 170.9, 63.4, 40.5, 21.3, 20.9 ppm.

2-methyl-3-(trimethylsilyl)propanal (product of 7): Enantiomeric excess was determined by GC with a Supelco’s Beta Dex 225 column, Temperature program: 100 °C, 1 °C/min to 120 °C, Flow rate = 1.0 mL/min, $t_{\text{major}} = 6.9$ min, $t_{\text{minor}} = 7.1$ min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 9.56 (s, 1H), 2.38-2.31 (m, 1H), 1.13 (d, $J = 8.6$ Hz, 3H), 1.01-0.95 (m, 2H), 0.06 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 206.7, 44.4, 19.5, 18.0, 1.0 ppm.

4-(trimethylsilyl)butanal (product of 7): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 9.77 (s, 1H), 2.46 (t, $J = 7.2$ Hz, 2H), 1.65 (tt, $J = 8.4, 7.2$ Hz, 2H), 0.53 (t, $J = 8.4$ Hz, 2H), 0.01 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 204.8, 49.3, 18.7, 18.4, 0.02 ppm.

2-methyl-3-phenylpropanal (product of 8): Enantiomeric excess was determined by GC with a Supelco’s Beta Dex 225 column, Temperature program: 95 °C, 60 mins, 5 °C/min to 140 °C, 10 mins, Flow rate = 1.0 mL/min, $t_{\text{minor}} = 53.2$ min, $t_{\text{major}}$
= 54.0 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 9.70 (s, 1H), 7.31-7.27 (m, 2H), 7.23-7.16 (m, 3H), 3.08 (dd, $J$ = 13.2, 5.6 Hz, 1H), 2.71-2.64 (m, 1H), 2.59 (dd, $J$ = 13.2, 5.6 Hz, 1H), 1.09 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 204.3, 138.9, 129.0, 128.5, 126.4, 48.1, 36.7, 13.2 ppm.

### 4-phenylbutanal (product of 8): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 9.80 (s, 1H), 7.31-7.27 (m, 2H), 7.23-7.16 (m, 3H), 2.67 (t, $J$ = 7.6 Hz, 2H), 2.45 (t, $J$ = 7.2 Hz, 2H), 1.96 (tt, $J$ = 7.6, 7.2 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 202.2, 141.2, 129.0, 128.5, 126.1, 43.2, 35.0, 23.7 ppm.

### (S)-3-(tert-butoxycarbonylamino)-2-methylpropanoic acid (9):$^{20}$ To a stirred solution of (S)-tert-butyl (2-methyl-3-oxopropyl)carbamate (2a) (374 mg, 2.0 mmol) in tert-butyl alcohol/water (5:1, 20 mL) were added successively NaH$_2$PO$_4$·2H$_2$O (528 mg, 3.4 mmol), 2-methyl-2-butene (1.49 mL, 14.0 mmol), and NaClO$_2$ (634 mg, 7.0 mmol). The resulting mixture was stirred for 5 h. The solvent was removed under reduced pressure. The residue was extracted with ethyl acetate, washed with water and brine, and dried over MgSO$_4$. The combined organic layers were concentrated under reduced pressure to give 9 (389 mg, 96% yield) as a viscous oil (>95% purity by $^1$H NMR analysis). The crystals were obtained by dissolving the oil in minimum CH$_2$Cl$_2$, adding hexanes (20 mL) and then standing in the freezer. $[\alpha]_{24}^D$ = 26.1 (c = 1.5, CHCl$_3$) at 94% ee; (R): lit.$^{[21]}$ $[\alpha]_{23}^{21}D$ = -25.5 (c = 1.41, CHCl$_3$); Enantiomeric excess was determined according to literature.$^{22}$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 5.09 (br,
$^1$H, 3.39 (m, 1H), 3.28 (m, 1H), 2.71 (m, 1H), 1.44 (s, 9H), 1.21 (d, $J = 7.2$ Hz, 3H); $^{13}$C
NMR (100 MHz, CDCl$_3$) $\delta$: 181.9, 156.9, 81.4, 43.2, 40.6, 28.7, 15.2 ppm.

(S)-tert-butyl (3-hydroxy-2-methylpropyl)carbamate

(10):

To a cooled solution of (S)-tert-butyl (2-methyl-3-oxopropyl)carbamate (2a) (187 mg, 1.0 mmol) in 20 mL of MeOH was added NaBH$_4$ (40 mg, 1.1 mmol) in portions at 0 ºC. After stirring at room temperature for 1h, the reaction mixture was quenched with saturated aqueous NH$_4$Cl (10 mL) and extracted 3 times with ethyl acetate (30 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$, the solvents were removed under reduced pressure. The crude product was purified by silica-gel column chromatography (Hexanes/EtOAc = 2:1) to yield 10 (180 mg, 95% yield) as a colorless oil. [$\alpha$]$^{24}_D$ = 12.1 (c = 1.0, CHCl$_3$) at 94% ee; (R); lit.[21] [$\alpha$]$^{23}_D$ = -25.5 (c = 1.41, CHCl$_3$); Enantiomeric excess was determined according to literature;\textsuperscript{22} $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 5.09 (br, 1H), 3.57 (m, 1H), 3.28 (m, 1H), 3.15 (m, 1H), 2.99 (m, 1H), 1.74(m, 1H), 1.41 (s, 9H), 0.82 (d, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 157.6, 79.6, 64.5, 43.0, 36.4, 28.5, 14.6 ppm.\textsuperscript{23}
References


Chapter 4

Synthesis and Applications of Tetraphosphorus Ligands in Linear-Selective Hydroformylation

4.1 Introduction

Hydroformylation of olefins to afford aldehydes is one of the most important homogeneous catalytic reactions that have been widely applied in industry. It is capable to transform olefins to products containing an aldehyde group that are versatile intermediates and building blocks for various pharmaceuticals, agrochemicals, commodity and fine chemicals.\(^1\) Production volumes obtained by using this process are estimated to be over nine million tons annually. For example, the normal aldehydes products of hydroformylation of propylene are improtant start materials to of polymer plasticizers and detergents.\(^{1a}\) As shown in Scheme 4-1, the linear product, \(n\)-butanal, is transformed into 2-ethylhexanol (2-EH) through consecutive aldol condensation and reduction. 2-EH reacts with phthalic anhydride to give bis(2-ethylhexyl) phthalate (DEHP), which is a important plasticizer to make PVC flexible with approximately annual output of three billion kilograms.
Scheme 4-1: Application of Hydroformylation in Industry.

One of the key issues in the hydroformylation process is the control of regiochemistry since the linear aldehydes are the desired intermediates for polymer and detergent industries. At early stage, most commercial hydroformylation processes use highly reactive rhodium catalysts that are modified with monophosphorus ligands, such as triphenylphosphine, to make the linear aldehydes dominate in products. Since the late eighties, a large amount of research has been devoted to the development of bisphosphorus ligands for rhodium-catalyzed linear-selective hydroformylation. There is a number of catalyst system based on diphosphine and diphosphite ligands giving highly regioselective linear aldehydes. Bisbi\textsuperscript{2} reported by Eastman Kodak company and Biphephos\textsuperscript{4} reported by Union Carbide company represent the two earliest bisphosphorus ligands applied in hydroformylation (as shown in Figure 4-1). Some other elegant examples include van Leeuwen's Xantphos\textsuperscript{4}, Beller's Naphos\textsuperscript{5}, calix[4]arene
bisphosphite,\textsuperscript{6} pyrrole-based bisphosphoramidite,\textsuperscript{7} and self-assembled bisphosphine ligands.\textsuperscript{8}

Although the above ligands have promoted the regioselectivity of hydroformylation to a high level, it is still highly desired to develop new ligands which can provide even higher linear/branched ratio under mild reaction condition. Another challenging point in this area is the hydroformylation of internal olefins to produce linear aldehydes, which is so-called isomerization-hydroformylation. Since internal olefins are cheaper and more readily available feedstock than terminal olefins, the development of highly selective and active catalysts for internal olefins is of great importance from the economic and energy points of view. On the other hand, the development of regioselective ligands for high-temperature hydroformylation is also of great significance from the view of industrial applications, since high temperatures always afford higher reaction rates.

In this chapter, we would like to report the design and synthesis of a series of new tetraphosphorus ligands 1 and 2 (Figure 4-1) as well as their applications in highly linear-selective hydroformylation. Comparing to their corresponding bisphosphorus ligands, tetraphosphorus ligands can dramatically increase the regioselectivities. In particular, tetraphosphoramidite ligand 1 obtained the highest regioselectivity ever reported in the isomerization-hydroformylation of internal olefins (\(n:i\) up to 51.7 for 2-octene and up to 80.6 for 2-hexene). The class of tetraphosphine ligands 2 provide high linear-selectivity for the hydroformylation of terminal olefins at very high temperature (\(n:i\) up to 87.9 for 1-hexene at 140 °C).
4.2 Results and Discussion

4.2.1 Design of Tetraphosphorus Ligands

One of the major issues that impair the regioselectivity of Rh-catalyzed hydroformylation reactions is the dissociation of phosphorus ligands from the metal center which leads to the formation of unselective catalytic species, especially at high
temperature. As elucidated in Scheme 4-2, for hydroformylation based on monophosphorus ligands, the effectively regioselective catalytic species is the one with two phosphines coordinated to the metal center. However, carbon monoxide is a strong $\pi$ acid that competes to bind to the rhodium center with the phosphorus ligand. The replacement of phosphine with CO leads to the formation of highly reactive yet unselective catalytic species. This exchange is accelerated at high temperature. To maintain the adequate concentration of the selective catalytic species, a large excess of monophosphorus ligands are usually employed in the industrial process. Using bisphosphorus ligands can improve the selectivity a lot, which may partly arise from the formation of more selective, bulky, and robust catalytic species (Scheme 4-2). Even if one phosphorus atom dissociates from the metal center, the another one still keeps the whole ligand molecule attached to the catalytic center, which impedes the formation of unselective catalytic species.

Scheme 4-2: Ligand Dissociation in Rhodium-Catalyzed Hydroformylation.
Considering the better regioselectivity and lower catalyst loading of bisphosphorus ligands, we envisaged that introducing more coordinative phosphorus site onto the ligands may further enhance their regioselectivity. Herein, we introduced a new strategy to enhance the chelating ability of ligand by using a novel symmetric tetraphosphorus ligand capable of forming multiple chelating modes. As shown in Scheme 4-3, there are four possible identical bidentate chelating manner when a tetraphosphorus ligand is complexed with rhodium, which can increase the concentration of the selective catalytic species. In addition, the nearby intramolecular free phosphorus atoms can effectively increase the local phosphorus concentration around the metal center and enhance the chelating ability. When a phosphine moiety in the bidentate ligand dissociates from the metal, two intermediates are formed by recoordination of another two phosphine moieties to the Rh center to reform the bidentate system. Such “enhanced multidentarity” has been demonstrated to enhance the ligands ability to stabilize catalytic systems and promote their longevity in transition-metal-catalyzed coupling reactions. We envision that tetraphosphine ligand could afford better regioselectivity at high temperatures than its corresponding bisphosphine analogue.

Scheme 4-3: Multiple Chelating Modes of Tetraphosphorus Ligand.
4.2.2 Design and Synthesis of Tetraphosphoramidite Ligand 1

In the points of view of cost and energy saving, directly linear-selective hydroformylation of internal olefins attracts more attention, since internal olefins are cheaper and more readily available feedstock than terminal olefins. This methodology is called isomerization-hydroformylation. In the last decade, there are quite a few reports in these area including van Leeuwen’s Xantphos derivatives (normal/isomeric ratio \( n:i = 9.5 \) for 2-octene),\(^{10}\) Beller’s electron-withdrawing Naphos type ligands \((n:i = 10.1\) for 2-octene),\(^{5}\) and bulky phosphite ligands\(^{11}\) of UCC \((n:i = 19\) and 17 for 2-hexene and 2-octene, respectively) and DuPont/DSM \((n:i = 36\) for 2-hexene).

To obtain high regioselectivity in the isomerization-hydroformylation of internal olefins, a high isomerization rate of internal olefin to terminal olefin and high regioselectivity for the following hydroformylation of the terminal olefin are equally important. Pyrrole-based bisphosphoramidite ligand\(^{7}\) (3, Figure 4-1) has been reported to afford a fast isomerization rate for internal olefins and high regioselectivity for terminal olefins in rhodium-catalyzed hydroformylation reactions. The detailed mechanistic study suggested that the high regioselectivity achieved with ligand 3 was due to its high electron-withdrawing property rather than bite angle and steric hindrance.\(^{7}\) In the presence of ligand 3, branched rhodium-alkyl complexes prefer exclusive \(\beta\)-hydride elimination (leading to the formation of 2-olefins) to carbon monoxide insertion (leading to the formation of branched aldehydes), whereas linear rhodiumalkyl complexes undergo carbon monoxide insertion to form linear aldehydes. Thus, based on our new strategy of tetraphosphorus ligand and the unique electronic properties of \(N-\)
pyrrolylphosphorus ligand, we designed a tetraphosphoramidite ligand 1 and envisioned that it would be an effective ligand for linear-selective isomerization-hydroformylation.

The symmetric nature of ligand 1 leads to its straightforward synthesis, which makes its application practical (Scheme 4-4). Tetramethoxy biphenyl 4 was reported to be synthesized from 1,3-dimethoxy benzene by an FeCl₃ mediated oxidative coupling reaction.¹² We optimized the procedure by direct adding FeCl₃ powder in portions, instead of a cooled solution of FeCl₃ in anhydrous THF, and successfully enhanced the yield from 70 % to 95 %. Tetraol 5 was obtained in 91 % yield by deprotecting the aromatic methoxy moieties with boron tribromide. Reaction of chlorodipyrrolyphosphine with tetraol 5 in the presence of NEt₃ afforded the desired tetraphosphoramidite ligand 1 in 36 % yield. The resulting tetraphosphoramidite ligand 1 is an air stable crystalline white solid that allows the hydroformylation reaction to be practicable process.

Scheme 4-4: The Synthesis of Tetraphosphoramidite Ligand 1.
To confirm the actual configuration of tetraphosphoramidite ligand 1, a single crystal of it was cultured by solvent diffusion from dichloromethane to hexane. The X-ray analysis of the crystal was displayed by ORTEP drawing in Figure 4-2. The structural analysis showed that the dihedron angle of the two phenyl rings in backbone are not exactly 90° (\(<\text{C}(5)\)-\text{C}(6)\)-\text{C}(7)\)-\text{C}(12) = -65.2°(2) ). The four \(N\)-pyrrolephosphosramidite moieties was distributed toward four different direction. It is believed that the C-C single bond in the biphenyl can rotate flexibly in some extent. These features make ligand 1 meet the requirement for multiple chelating modes.

Figure 4-2: ORTEP Representation of Ligand 1 at 50% Probability for The Drawing of Thermal Ellipsoids (Solvents and Hydrogen Atoms Are Omitted for Clarity).
4.2.3 Hydroformylation Reactions with Tetraphosphoramidite Ligand 1

With tetraphosphoramidite ligand 1 in hand, we set out to optimize the reaction condition for isomerization-hydroformylation using 2-octene as the standard substrate. The catalyst were prepared in situ by mixing ligand 1 with Rh(acac)(CO)₂ at certain ratios in toluene. The reactions were carried out with decane as the internal standard, a substrate/catalyst ratio of 10 000, and a rhodium concentration of 0.57 mM. The results are summarized in Table 4-1. The ligand/metal ratio has a remarkable effect on the isomerization-hydroformylation reaction (Table 4-1, entries 1-3). Increasing the ligand/metal ratio from 1:1 to 4:1 resulted in much higher regioselectivity but lowered down the reaction rate. A minimum ligand/metal ratio of 2 is essential to achieve high regioselectivity. Further increasing the ligand/metal ratio did not significantly improve the regioselectivity. The reaction temperature also plays a key role in isomerization-hydroformylation (Table 4-1, entries 4-7). Although high regioselectivity was obtained at low temperature, the reaction rate was quite low. A high temperature (100 °C) is necessary to achieve acceptable regioselectivity with a high reaction rate. The effect of the pressure of CO/H₂ was also investigated (Table 4-1, entries 8-10). The lower pressure generally resulted in higher reaction rate and regioselectivity. Decreasing the CO/H₂ pressure from 10/10 atm to 5/5 atm did not change the reaction rate very much; however, the regioselectivity was improved to some extent. Lengthening the reaction time to 12 h diminished the regioselectivity (n:i ratio dropped from 51.7 to 38, Table 4-1, entries 10-11). The decreased reactivity can be explained by lower isomerization rate resulted from decreased concentration of internal olefins at high conversion.
Table 4-1: Isomerization-hydroformylation of 2-Octene with Ligand 1 under Different Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>L/Rh</th>
<th>T (˚C)</th>
<th>CO/H₂ (atm)</th>
<th>n:iᵇ</th>
<th>Normal (%)ᶜ</th>
<th>TONᵈ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1</td>
<td>100</td>
<td>10/10</td>
<td>17.7</td>
<td>94.7</td>
<td>1.8 x10³</td>
</tr>
<tr>
<td>2</td>
<td>2:1</td>
<td>100</td>
<td>10/10</td>
<td>43.4</td>
<td>97.7</td>
<td>1.5 x10³</td>
</tr>
<tr>
<td>3</td>
<td>4:1</td>
<td>100</td>
<td>10/10</td>
<td>46</td>
<td>97.9</td>
<td>1.5 x10³</td>
</tr>
<tr>
<td>4</td>
<td>3:1</td>
<td>120</td>
<td>10/10</td>
<td>30.4</td>
<td>96.8</td>
<td>3.4 x10³</td>
</tr>
<tr>
<td>5</td>
<td>3:1</td>
<td>100</td>
<td>10/10</td>
<td>46</td>
<td>97.9</td>
<td>1.6 x10³</td>
</tr>
<tr>
<td>6</td>
<td>3:1</td>
<td>80</td>
<td>10/10</td>
<td>47.7</td>
<td>97.9</td>
<td>7.7 x10²</td>
</tr>
<tr>
<td>7</td>
<td>3:1</td>
<td>60</td>
<td>10/10</td>
<td>53.7</td>
<td>98.2</td>
<td>1.4 x10³</td>
</tr>
<tr>
<td>8</td>
<td>3:1</td>
<td>100</td>
<td>30/30</td>
<td>24.3</td>
<td>96</td>
<td>3.1 x10²</td>
</tr>
<tr>
<td>9</td>
<td>3:1</td>
<td>100</td>
<td>20/20</td>
<td>30</td>
<td>96.8</td>
<td>5.1 x10²</td>
</tr>
<tr>
<td>10</td>
<td>3:1</td>
<td>100</td>
<td>5/5</td>
<td>51.7</td>
<td>98.1</td>
<td>1.5 x10³</td>
</tr>
<tr>
<td>11ᵉ</td>
<td>3:1</td>
<td>100</td>
<td>5/5</td>
<td>38</td>
<td>97.4</td>
<td>7.7 x10³</td>
</tr>
</tbody>
</table>

ᵃ S/C = 10000, [Rh] = 0.57 mM, t = 1 h, toluene as solvent, decane as internal standard.;b Normal/isomeric ratio, determined based on GC.ᶜ Percentage of normal aldehyde in all aldehydes.ᵈ Turnover number, determined based on GC.ᵉ Reaction time was 12 h.
With the optimized reaction conditions (100 °C, CO/H₂ = 5/5 atm, ligand/metal ratio = 3, 1 h reaction time), we compared the tetraphosphoramidite ligand 1 with the corresponding bisphosphorus ligand 3 side by side in the isomerization-hydroformylation of 2-olefins (Table 4-2). The results showed that tetraphosphoramidite ligand 1 afforded much better regioselectivities than bisphosphorus ligand 3 in the isomerization-hydroformylation. The $n:i$ ratio is 51.7 for ligand 1 while that for ligand 3 is only 10.1 (Table 4-2, entries 1-2).

### Table 4-2: Isomerization-hydroformylation of Internal Olefins with Ligand 1 and 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>L</th>
<th>$n:i^b$</th>
<th>Normal (%)$^c$</th>
<th>TON$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-octene</td>
<td>1</td>
<td>51.7</td>
<td>98.1</td>
<td>1.5 x10³</td>
</tr>
<tr>
<td>2</td>
<td>2-octene</td>
<td>3</td>
<td>10.1</td>
<td>91</td>
<td>2.3 x10³</td>
</tr>
<tr>
<td>3</td>
<td>2-hexene</td>
<td>1</td>
<td>80.6</td>
<td>98.8</td>
<td>1.7 x10³</td>
</tr>
<tr>
<td>4</td>
<td>2-hexene</td>
<td>3</td>
<td>15</td>
<td>93.8</td>
<td>2.1 x10³</td>
</tr>
</tbody>
</table>

$^a$ S/C = 10000, [Rh] = 0.57 mM (for 2-octene) or 0.69 mM (for 2-hexene), Ligand/Rh ratio = 3:1, temperature = 100°C, CO/H₂ = 5/5 atm, toluene as solvent, decane as internal standard. $^b,c,d$ See Table 4-1.

Hydroformylation of terminal olefins with tetraphosphorus ligand 1 was then investigated. First of all, the optimization of reaction condition was carried our with 1-
octene as the standard substrate (as summarized in Table 4-3). Temperature influenced the hydroformylation reaction very much: high temperatures led to higher reaction rates and higher isomerization, but lower regioselectivity (Table 4-3, entries 1-4). For example, the \( n:i \) ratio was 461 at 40 °C, whereas this number decreased to 236 (still a very high value) at 100 °C. Since hydroformylation of terminal olefins at high temperatures resulted in the formation of a high percentage of isomerization products, a low temperature (80 °C) was preferred. The effects of total pressure of CO/H\(_2\) (pressure ranging from 5/5 to 30/30 atm) were also evaluated. Low pressure generally results in slightly decreased reactivity, but leads to higher regioselectivity and isomerization percentage.

Table 4-3: Hydroformylation of 1-Octene with Ligand 1 under Different Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>CO/H(_2) (atm)</th>
<th>n:i(^b)</th>
<th>Normal (%)(^c)</th>
<th>Isomerization (%)(^d)</th>
<th>TON(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>10/10</td>
<td>236</td>
<td>99.6</td>
<td>21.6</td>
<td>7.6 x10(^3)</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>10/10</td>
<td>372</td>
<td>99.7</td>
<td>15.3</td>
<td>6.9 x10(^3)</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>10/10</td>
<td>442</td>
<td>99.8</td>
<td>5.4</td>
<td>3.5 x10(^3)</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>10/10</td>
<td>461</td>
<td>99.8</td>
<td>3.9</td>
<td>0.64 x10(^3)</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>30/30</td>
<td>242</td>
<td>99.6</td>
<td>8</td>
<td>7.7 x10(^3)</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>5/5</td>
<td>405</td>
<td>99.8</td>
<td>28.3</td>
<td>6.2 x10(^3)</td>
</tr>
</tbody>
</table>

\(^{a}\) S/C = 10000, [Rh] = 0.2 mM, ligand/Rh ratio = 3:1, reaction time = 1 h, toluene as solvent, decane as internal standard. \(^{b,c,e}\) See Table 4-1. \(^{d}\) Isomerization to 2-octene.
For comparison, hydroformylation of terminal olefins with bisphosphorus ligand $3$ was also conducted (Table 4-4). As in the case of hydroformylation of internal olefins, the tetraphosphoramidite ligand $1$ afforded higher regioselectivity than the bisphosphorus ligand $3$ did both for 1-octene and 1-hexene. As high as $n:i$ of 372 was achieved for hydroformylation of 1-octene with ligand $1$. To the best of our knowledge, this is the highest value ever reported.

Table 4-4: Hydroformylation of Terminal olefins with ligand $1$ and $3^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>L</th>
<th>$n:ib$</th>
<th>Normal (%)$^c$</th>
<th>Isomerization (%)$^d$</th>
<th>TON$^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-octene</td>
<td>1</td>
<td>372</td>
<td>99.7</td>
<td>15.3</td>
<td>6.9 x10$^3$</td>
</tr>
<tr>
<td>2</td>
<td>1-octene</td>
<td>3</td>
<td>74.1</td>
<td>98.7</td>
<td>10</td>
<td>8.4 x10$^3$</td>
</tr>
<tr>
<td>3</td>
<td>1-hexene</td>
<td>1</td>
<td>382</td>
<td>99.7</td>
<td>18.7</td>
<td>6.7 x10$^3$</td>
</tr>
<tr>
<td>4</td>
<td>1-hexene</td>
<td>3</td>
<td>80.8</td>
<td>98.8</td>
<td>12.2</td>
<td>7.9 x10$^3$</td>
</tr>
</tbody>
</table>

$^a$ S/C = 10000, [Rh] = 0.2 mM, ligand/Rh ratio = 3:1, temperature = 80 °C, CO/H$_2$ = 10/10 atm, reaction time = 1h, toluene as solvent, decane as internal standard. $^b,c,e$ See Table 4-1. $^d$ Isomerization to 2-olefin.

4.2.4 Design and Synthesis of Tetraphosphine Ligands 2

Although the tetraphosphoramidite ligand $1$ afforded efficient reactivity and very high regioselectivity in the hydroformylation of both terminal and internal olefins, a high level of isomerization was observed at high temperature in the hydroformylation of...
terminal olefins. Thus, it is desirable to develop highly regioselective ligands with less isomerization rate for high-temperature hydroformylation. Another challenge that is important to industry is the hydroformylation of long chained olefins; in these cases, the produced aldehydes have high boiling points and thus require high-temperature distillation during the production process, which means that the ligands used in the reaction must be tolerant towards high temperatures. Since hydroformylation with more electron-donating bisphosphines such as Bisbi\(^2\) is less likely to undergo isomerization, a class of tetraphosphine ligands 2 was then designed based on a biphenyl backbone (Figure 4-1) for the hydroformylation of terminal olefins.

The synthesis of ligands 2a-e was realized as shown in Scheme 4-5. Starting from the ozonolysis of pyrene, reduction of tetracarbaldehyde 6 by sodium borohydride and bromination of 2,2',6,6'-tetrakis(hydroxymethyl)-biphenyl 7, tetrabromide 8 was prepared in high yields.\(^1\) Whereas the synthesis of Bisbi by reaction of lithium diphenylphosphine with 2,2'-bisbromomethyl-1,1'-biphenyl was reported to occur in high yield,\(^2\) the reaction of tetrabromide 8 with lithium diphenylphosphine gave a complex mixture of unidentified products as monitored by \(^{31}\)P NMR spectroscopy \textit{in situ}. To overcome this problem, we converted tetrabromide 8 into the less reactive tetrachloride 9 by the reaction of the tetrabromide with lithium chloride in DMF at room temperature; the tetrachloride 9 was obtained in high yield (93%). We were pleased to find that the reaction of tetrachloride 9 with lithium diarylphosphine\(^1\) cleanly afforded the desired tetraphosphine as indicated by a single peak in \textit{in situ} \(^{31}\)P NMR spectra. Since tetraphosphines 2 are air-sensitive compounds, they were protected \textit{in situ} with borane
for purification. A simple deprotection of the borane with 1,4-diazabicyclo[2.2.2]octane (DABCO) afforded the desired tetraphosphine ligands 2a-e in 64-79% yields.

Scheme 4-5: The Synthesis of Tetraphosphine Ligands 2a-e.

Because the ozonolysis process is not very accessible and practicable in laboratory and industry, we optimized the synthetic route to avoid the use of ozone (Scheme 4-6). Tetracarboxylic acid 11 was first prepared by the oxidation of pyrene with RuCl₃/NaIO₄ catalytic system. However, an attempt to reduce tetracarboxylic acid 11 with LiAlH₄ in THF under refluxing condition did not give desired tetraol, which is may due to the poor solubility of tetracarboxylic acid 11 in THF. To our delight, the
acetychloride derivative of 11 could be reduced into tetraol 7 successfully in 73 % yield. We also found that the tetrabromide intermediate is not necessary. Tetrachloride 9 could be obtained by direct treatment of tetraol 7 with thionyl chloride. To the end, the final ligand 2f was prepared avoiding the boron-protection step in a high yield (82 %).

![Scheme 4-6: The Optimized Synthesis of Tetraphosphine Ligand 2f.](image)

4.2.5 Hydroformylation of Terminal Olefins with Tetraphosphine Ligands 2

Before tetraphosphine ligands 2a-f were applied in hydroformylation of terminal olefins, the reaction conditions were optimized in one hour run with ligand 2a as representative, 1-octene as the standard substrate, decane as internal standard and toluene as solvent. The rhodium catalyst was prepared in situ by mixing the ligand 2a with Rh-(acac)(CO)₂ in toluene. The substrate/catalyst ratio was 2000 and the catalyst concentration was 1.0 mM.
The effects of the ligand/metal ratio on hydroformylation of terminal olefins with the tetraphosphine ligand 2a were examined. As shown in Table 4-5 (entries 1-4), a slight decrease in both the \( n:i \) ratio and isomerization were observed when the ligand/metal ratio was increased from 1:1 to 6:1. The effects of reaction temperature on the hydroformylation reaction were also investigated (Table 4-5, entries 3, and 5-7). To our delight, only a slight decrease in the \( n:i \) ratio was observed when the reaction temperature was increased from 100 to 140 °C. As expected, hydroformylation at lower temperatures led to less olefin isomerization. Finally, the effects of CO/H\(_2\) pressure were tested (Table 4-5, entries 3, 8-10). At high CO/H\(_2\) pressure, the regioselectivities were low, however, the regioselectivities could be increased by lowering the CO/H\(_2\) pressure. The highest regioselectivity (\( n:i \) ratio of 66.7) was obtained under a CO/H\(_2\) pressure of 5/5 atm. However, a significant amount of isomerization was observed under this pressure, indicating that low CO/H\(_2\) pressures facilitate the olefin isomerization.
Table 4-5: Hydroformylation of 2-Octene with Ligand 2a under Different Reaction Conditions.\textsuperscript{a}

\[
\begin{align*}
\text{n-C}_6\text{H}_{13} & \quad \xrightarrow{[\text{Rh}]/\text{ligand } 2\text{a}} \quad \text{n-C}_6\text{H}_{13} \text{CHO} + \text{n-C}_6\text{H}_{13} \text{CHO} \\
& \quad \xrightarrow{\text{CO/H}_2} 
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>L/Rh</th>
<th>T (˚C)</th>
<th>CO/H\textsubscript{2} (atm)</th>
<th>n:i\textsuperscript{b}</th>
<th>Normal (%)\textsuperscript{c}</th>
<th>Isomer. (%)\textsuperscript{d}</th>
<th>TON\textsuperscript{e}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1</td>
<td>100</td>
<td>10/10</td>
<td>53.7</td>
<td>98.2</td>
<td>7.9</td>
<td>1.8 x10\textsuperscript{3}</td>
</tr>
<tr>
<td>2</td>
<td>2:1</td>
<td>100</td>
<td>10/10</td>
<td>53.4</td>
<td>98.2</td>
<td>7.3</td>
<td>1.8 x10\textsuperscript{3}</td>
</tr>
<tr>
<td>3</td>
<td>4:1</td>
<td>100</td>
<td>10/10</td>
<td>50.5</td>
<td>98.1</td>
<td>5.6</td>
<td>1.8 x10\textsuperscript{3}</td>
</tr>
<tr>
<td>4</td>
<td>6:1</td>
<td>100</td>
<td>10/10</td>
<td>48.9</td>
<td>98.0</td>
<td>5.6</td>
<td>1.8 x10\textsuperscript{3}</td>
</tr>
<tr>
<td>5</td>
<td>4:1</td>
<td>140</td>
<td>10/10</td>
<td>45.2</td>
<td>97.8</td>
<td>6.5</td>
<td>1.8 x10\textsuperscript{3}</td>
</tr>
<tr>
<td>6</td>
<td>4:1</td>
<td>120</td>
<td>10/10</td>
<td>49.8</td>
<td>98.0</td>
<td>5.8</td>
<td>1.8 x10\textsuperscript{3}</td>
</tr>
<tr>
<td>7</td>
<td>4:1</td>
<td>80</td>
<td>10/10</td>
<td>34.2</td>
<td>97.2</td>
<td>3.4</td>
<td>1.4 x10\textsuperscript{3}</td>
</tr>
<tr>
<td>8</td>
<td>4:1</td>
<td>100</td>
<td>30/30</td>
<td>16.5</td>
<td>94.3</td>
<td>2.9</td>
<td>1.2 x10\textsuperscript{3}</td>
</tr>
<tr>
<td>9</td>
<td>4:1</td>
<td>100</td>
<td>20/20</td>
<td>22.3</td>
<td>95.7</td>
<td>3.0</td>
<td>1.2 x10\textsuperscript{3}</td>
</tr>
<tr>
<td>10</td>
<td>4:1</td>
<td>100</td>
<td>5/5</td>
<td>66.7</td>
<td>98.5</td>
<td>17.3</td>
<td>1.6 x10\textsuperscript{3}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reagents and conditions: S/C = 2000, [Rh] = 1.0 mM, t = 1 h, toluene as solvent, decane as internal standard. \textsuperscript{b,c} See Table 4-1. \textsuperscript{d} Isomerization to internal olefin. \textsuperscript{e} Turnover number, determined by GC analysis.
For comparison, bisphosphine ligand Bisbi was prepared and employed in the hydroformylation of terminal olefins under the same reaction conditions. The results, summarized in Table 4-6, clearly show that, in all cases, the use of tetraphosphine ligand 2a afforded higher regioselectivities than Bisbi under the same reaction conditions. It should be noted that, at high temperature, a dramatic decrease in the regioselectivity and a high percentage of isomerization was observed with bisphosphine ligand Bisbi (Table 4-6, entries 2 and 8). For example, in the hydroformylation of 1-octene, the regioselectivity was much lower ($n:i = 2.4$) and the extent of isomerization was significant (24%) at 140 °C with Bisbi as ligand (Table 4-6, entry 2); whereas, the regioselectivity remained high ($n:i = 45.2$) and the isomerization remained low (6.5%) using tetraphosphine ligand 2a at the same temperature (Table 4-6, entry 1). At lower temperature (100 °C), both tetraphosphine 2a and bisphosphine Bisbi afforded high regioselectivity and low isomerization, with $n:i$ ratios greater than 40 and isomerization less than 10% (Table 4-6, entries 5, 6, 11, and 12). The similar performances with both ligands at low temperature and dramatic differences observed at high temperature suggest that the superior performance of ligand 2a at high temperature is indeed due to the enhanced chelating ability of ligands 2. This result is also important from the practical point of view because highly regioselective hydroformylation can, under these conditions, now be carried out at higher temperature, with subsequently higher reaction rates.
Table 4-6: Comparison of tetraphosphine and bisphosphine ligands.\textsuperscript{a}

\[
\begin{array}{cccccccc}
\text{Entry} & \text{Substrate} & \text{T (°C)} & \text{L} & n:i & \text{Normal}^c & \text{Isomer.}^d & \text{TON}^e & \text{TOF}^f \\
1 & 1-octene & 140 & 2a & 45.2 & 97.8 & 6.5 & 1.8 \times 10^3 & 9.3 \times 10^3 \\
2 & 1-octene & 140 & Bisbi & 2.4 & 70.6 & 24 & 1.5 \times 10^3 & 6.2 \times 10^3 \\
3 & 1-octene & 120 & 2a & 49.8 & 98.0 & 5.8 & 1.8 \times 10^3 & 7.3 \times 10^3 \\
4 & 1-octene & 120 & Bisbi & 29.5 & 96.7 & 8.7 & 1.8 \times 10^3 & 5.7 \times 10^3 \\
5 & 1-octene & 100 & 2a & 50.5 & 98.1 & 5.6 & 1.8 \times 10^3 & 2.5 \times 10^3 \\
6 & 1-octene & 100 & Bisbi & 45.2 & 97.8 & 6.7 & 1.6 \times 10^3 & 3.4 \times 10^3 \\
7 & 1-hexene & 140 & 2a & 43.8 & 97.8 & 7.7 & 1.8 \times 10^3 & 9.5 \times 10^3 \\
8 & 1-hexene & 140 & Bisbi & 4.9 & 83.1 & 20 & 1.6 \times 10^3 & 8.7 \times 10^3 \\
9 & 1-hexene & 120 & 2a & 48.5 & 98.0 & 7.1 & 1.8 \times 10^3 & 6.6 \times 10^3 \\
10 & 1-hexene & 120 & Bisbi & 35.8 & 97.3 & 9.1 & 1.8 \times 10^3 & 6.0 \times 10^3 \\
11 & 1-hexene & 100 & 2a & 48.6 & 98.0 & 6.6 & 1.8 \times 10^3 & 3.3 \times 10^3 \\
12 & 1-hexene & 100 & Bisbi & 43.2 & 97.7 & 9.4 & 1.7 \times 10^3 & 2.6 \times 10^3 \\
\end{array}
\]

\textsuperscript{a} Reagents and conditions: S/C = 2000, ligand/Rh ratio = 4:1, [Rh] = 1.0 mM, \( t = 1 \) h, CO/H2 (10/10 atm), toluene as solvent, decane as internal standard.\textsuperscript{b,c,d,e} See Table 4-5.\textsuperscript{f}

Turnover frequency, determined by GC analysis, reaction time = 10 min.
Ligands 2b-f were then applied to rhodium-catalyzed hydroformylation of terminal olefins 1-hexene and 1-octene under a range of reaction temperatures (Tables 4-7 and 4-8). It was found that the introduction of substituents at the diphenylphosphine moiety of 2a affected both the regioselectivity of the aldehydes and the activity of the catalytic system. In both cases, the catalytic system with ligands 2b, 2c, 2e, and 2f, which contain electron-withdrawing substituents, showed higher activity than with ligand 2d, which contains an electron-donating group. The trend for those ligands on the regioselectivity, however, was not as clear. Whereas ligand 2b afforded the best linear to branch ratio at 140 °C for 1-hexene (87.9), ligand 2f was found to be somewhat better than 2b for 1-octene under similar reaction conditions (52.4 versus 47.4) (Table 4-7, entry 1, and Table 4-8, entries 1 and 11). The position of the substituents may also exert some influence on the regioselectivity. Ligand 2c, containing a trifluoromethyl substituent at the para-position of the diphenylphosphine moiety, gave a higher linear to branch ratio for the hydroformylation of the 1-hexene than the corresponding ligand 2e with the same substituent at the meta-position (Table 4-7, entries 4 and 9). Apparently, ligand 2e has a larger steric effect than ligand 2c. This effect was reversed when 1-octene was examined (Table 4-8, entries 4 and 9). With one more trifluoromethyl substituent at the meta-position of the diphenylphosphine moiety, the increase in the regioselectivity observed for the reaction with 1-octene was continued, whereas that with 1-hexene decreased (Table 4-7, entry 11 and Table 4-8, entry 11). From these results, it can clearly be seen that subtle changes in the substrate chain length can require a change in the choice of suitable ligand.
Table 4-7: Hydroformylation of 1-Hexene with Tetraphosphine Ligands 2b-f at A Range of Temperatures.\textsuperscript{a}

\[ \text{n-C}_6\text{H}_{11} \rightarrow [\text{Rh}]/\text{Ligand L} \xrightarrow{\text{CO/H}_2} \text{n-C}_6\text{H}_{11}-\text{CHO} + \text{n-C}_6\text{H}_{11}-\text{CHO} \]

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\textsuperscript{a,b,c,d,e} See Table 4-6.
Table 4-8: Hydroformylation of 1-Octene with Tetraphosphine Ligands 2b-f at A Range of Temperatures.\(^a\)

\[
\begin{align*}
\text{n-C}_\text{8} \text{H}_{13} & \quad \overset{[\text{Rh} / \text{ligand} \; \text{L}]}{\text{CO} / \text{H}_2} & \quad \text{n-C}_\text{8} \text{H}_{13} \text{CHO} + \text{n-C}_\text{8} \text{H}_{13} \text{CHO} \\
\end{align*}
\]

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<th>Normal (%)(^c)</th>
<th>Isomer. (%)(^d)</th>
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\(^{a,b,c,d,e}\) See Table 4-6.
4.3 Conclusion

In conclusion, a new strategy for ligand design in linear-selective hydroformylation was developed which was using tetraphosphorus ligands with multiple chelating modes to enhance chelating ability and regioselectivity comparing their corresponding bisphosphorus ligands. Based on this concept, two types of tetraphosphorus ligands, tetraphosphoramidite ligand 1 and tetraphosphine ligands 2a-f, were designed, synthesized and successfully applied in highly linear-selective hydroformylations. To the best of our knowledge, tetraphosphoramidite ligand 1 provides the highest regioselectivity ever reported in the hydroformylation of both internal olefins and terminal olefins. Tetraphosphine ligands 2 exhibited remarkably improved high temperature performance in the hydroformylation of terminal olefins. The steric and electronic effects of substituents on the diarylphosphine moiety were also examined. Further applications of the ligands and studies on the mechanism are under investigation.
Experimental Section

**General Methods:** All reactions and manipulations that were sensitive to moisture or air were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. Solvents were dried with standard procedures and degassed with N₂. Column chromatography was performed using 200-400 mesh silica gel supplied by Natland International Corp. Thin-layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. ¹H, ¹³C, and ³¹P NMR spectra were recorded in CDCl₃ or CD₂Cl₂ on Bruker Avance 400 MHz spectrometers or Varian Mercury 500 MHz FT-NMR spectrometer. HRMS were recorded on a Thermo LTQ Orbitrap hybrid mass spectrometer. GC analysis was carried out on Hewlett-Packard 6890 gas chromatography using chiral capillary columns. The single crystal X-ray analysis was carried out on Bruker-AXS Smart APEX CCD diffractometer.

**Synthesis of 2,2',6,6'-Tetramethoxy-biphenyl (4)**

![Structure of 2,2',6,6'-Tetramethoxy-biphenyl (4)](image)

To a 250 mL Schlenk flask was added 1, 3-dimethoxybenzene (8.26 g, 60.0 mmol). The flask was degassed and charged with nitrogen. To the flask was added THF (40 mL). The resulting solution was cooled to -78 °C in a dry ice/acetone bath. To the cooled solution was added n-BuLi (26.4 mL, 2.5 M solution in hexane, 66.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. the
mixture was cooled again to -78 °C and added anhydrous FeCl₃ powder (13.5 g, 83 mmol) by portions with vigorous stirring. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was concentrated under reduced pressure. To the residue was added aqueous 2N HCl solution (100 mL), CH₂Cl₂ (60 mL). After stirring for 5 min, the organic phase was separated. The organic phase was washed with aqueous 2N HCl solution (2 x 20 mL), dried over Na₂SO₄ and passed through a short silica gel plug. The pure title product was obtained by recrystallization from EtOH. (7.73 g, 95 %). ¹H NMR (300 Hz, CDCl₃) δ: 7.31 (t, J = 8.30 Hz, 2H), 6.68 (d, J = 8.33 Hz, 4H), 3.73 (s, 12H); ¹³C NMR (75 Hz, CDCl₃) δ: 158.3, 128.7, 112.4, 104.4, 56.1.

Synthesis of Biphenyl-2,2',6,6'-tetraol (5)

To a 250 mL Schlenk flask was added 2,2',6,6'-tetramethoxybiphenyl 4 (5.48 g, 20 mmol). The flask was degassed and charged with nitrogen. To the flask was added CH₂Cl₂ (100 mL). The resulting solution was cooled to -78 °C in a dry ice/acetone bath. To the cooled solution was added boron tribromide (7.7 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. After cooled to 0 °C, water (50 mL) was added dropwise to quench the reaction. The organic phase was separated and the aqueous phase was extracted with ether (3 x 25 mL). The combined
organic layers was dried over $\text{Na}_2\text{SO}_4$ and concentrated under reduced pressure. The crude product was purified by recrystallization from ethanol to give the title compound (3.57 g, 81%). $^1\text{H NMR}$ (300 Hz, $\text{CD}_2\text{Cl}_2$) $\delta$: 7.59 (s, 4H), 7.02 (t, $J = 8.13$ Hz, 2H), 6.48 (d, $J = 8.10$ Hz, 4H); $^{13}\text{C NMR}$ (75 Hz, $\text{CD}_2\text{Cl}_2$) $\delta$: 207.0, 157.2, 129.8, 108.1.

**Synthesis of 1,1′-Biphenyl-2,2′,6,6′-tetrakis-(dipyrrolylphosphoramidite) (1)**

![Chemical structure](image)

To a solution of chlorodipyrrolyphosphine (4.4 mmol, 0.87g) in THF (10 mL) was added dropwise triethylamine (1mL) and a solution of tetraol 5 (1 mmol, 0.218g) in THF (5 mL) at room temperature. The triethylamine·HCl salts were formed immediately after the addition. The reaction mixture was stirred for 6 h at room temperature. The triethylamine.HCl salts were then filtered off and the solvent was removed under vacuum. The crude product was purified by flash chromatography on basic aluminum oxide (eluting with hexane/EtOAc/NET$_3$ 6:1:0.1) to afford the pure ligand (0.31 g, 36%) as an air-stable colorless solid. $^1\text{H NMR}$ (300 Hz, $\text{CD}_2\text{Cl}_2$) $\delta$: 7.23 (t, $J = 8.3$ Hz, 2H), 6.68 (m, 20H), 6.21 (m, 16H); $^{13}\text{C NMR}$ (75 Hz, $\text{CD}_2\text{Cl}_2$) $\delta$: 152.86 (d, $J = 12.2$Hz) 131.0, 121.5 (d, $J = 16.8$Hz), 118.1, 115.3(d, $J = 13.7$ Hz), 112.7; $^{31}\text{P NMR}$ (146Hz, CDCl$_2$) $\delta$: 107.3. HRMS (ES$^+$) calcd. for C$_{44}$H$_{39}$N$_8$O$_4$P$_4$ [MH$^+$] 867.2045, found 867.2021.
Synthesis of Biphenyl-2,2',6,6'-tetracarboxaldehyde (6)

To a 1-L three-neck flask equipped with a magnetic stirrer, a gas inlet tube, and a drying tube was charged pyrene (10.0 g, 50 mmol) and dry CH₂Cl₂ (350 mL). The resulting solution was cooled to -78 °C in a dry ice/acetone bath. Ozone was introduced to the stirred solution at -78 °C for 2.5 h, and the temperature of the reaction mixture was maintained at -78 °C. The excess ozone was removed by bubbling oxygen through the solution for 5 min at -78 °C and stirred for another 1 h. A solution of sodium iodide (68.0 g) in glacial acetic acid (500 mL) was added dropwise during 1 h to the reaction mixture at -78 °C. After stirring for 30 min at -78 °C, the reaction mixture was allowed to warm gradually to 0 °C. The mixture was stored in a refrigerator (4 °C) for 24 h. The reaction mixture was successively washed with aqueous Na₂S₂O₃ (10%, 800 mL), aqueous NaHCO₃ (5%, 1.5 L), and water (500 mL) until the pH of aqueous layer = 7. The organic layer was then dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was dissolved in a minimum of CH₂Cl₂ and chromatographed on a silica gel column using n-hexane and CH₂Cl₂ as eluents. Pyrene was first eluted with n-hexane. It was followed by the tetraaldehyde which was eluted with CH₂Cl₂. The solvent was removed under reduced pressure. The crude product was recrystallized from toluene to give 6 as a bright yellow solid (6.4 g, 50%). ¹H NMR (300 MHz, CDCl₃) δ: 9.69 (s, 4H), 8.25 (d, J = 7.72 Hz, 4H), 7.84 (t, J = 7.66 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ: 189.72, 139.23, 135.83, 135.76, 129.94.
Synthesis of 2,2’,6,6’-Tetrakis( hydroxymethyl) Biphenyl (7)

To a mixture of tetracarboxaldehyde 6 (6.3 g, 23.7 mmol) in absolute methanol (150 mL) was added portionwise sodium borohydride (2.7 g, 75 mmol) under anhydrous conditions. The addition was completed in 1 h. The reaction mixture was heated to 40 °C and stirred for 4 h. The mixture became clear during the reaction. To the reaction mixture was added dropwise aqueous 9 % HCl solution until pH = 7. The neutralized solution was concentrated under reduced pressure. The residue was extracted with boiling isopropanol (3 x 150 mL). The combined extractions were concentrated under reduced pressure. The crude product was recrystallized from hot water to give 7 (6.0 g, 95 %) as a colorless plates. $^1$H NMR (300 MHz, CDCl$_3$) δ:7.45-7.42 (m, 4H), 7.36-7.31 (m, 2H), 4.72 (bs, 4H), 3.97 (s, 8H); $^{13}$C NMR (75MHz, CDCl$_3$) δ: 137.8, 132.7, 126.0, 125.2, 59.8.

Synthesis of 2,2’,6,6’-Tetrakis-bromomethyl-biphenyl (8)

To a solution of 2,2’,6,6’-tetrakis(hydroxymethyl) biphenyl 7 (5.0 g, 18.2 mmol) in CH$_2$Cl$_2$ (80 mL) was added dropwise a solution of phosphorus tribromide (30 mL,
excess) in CH₂Cl₂ (30 mL) under anhydrous conditions at room temperature. After the addition was completed, the reaction mixture was heated to reflux (bath temperature 50 °C) and stirred for 4 h. The reaction mixture was cooled to room temperature, and treated dropwise with water (80 mL). Caution: Hydrogen bromide was vigorously evolved during addition. After stirring for 5 min, the organic phase was separated, washed with water (3 x 30 mL) and dried over Na₂SO₄. The solvent was evaporated under reduced pressure. The residue was purified by recrystallization from hexane to afford 8 as a white solid (6.9 g, 72 %). ¹H NMR (300 MHz, CD₂Cl₂) δ: 7.64-7.61 (m, 4H), 7.56-7.51 (m, 2H), 4.25 (s, 8H); ¹³C NMR (75MHz, CD₂Cl₂) δ: 137.1, 135.6, 131.9, 130.4, 32.6.

Synthesis of 2,2′,6,6′-Tetrakis-chloromethyl-biphenyl (9)

To a solution of tetrabromide 8 (2.2 g, 4.2 mmol) in DMF (80 mL) was added LiCl (2.82 g, 67.2 mmol). The reaction mixture was stirred at room temperature for 6 h. After the reaction was complete, the reaction mixture was cooled to 0 °C. To the cooled mixture was then added carefully 5% aqueous HCl solution (30 mL) (exothermic reaction). After stirring for 5 min, the mixture was extracted with ether (4 x 40mL) and washed with saturated aqueous NaCl solution (80 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated to dryness. Pure product was obtained by recrystallization from CH₂Cl₂/hexanes as a white solid (1.35 g, 93% yield). ¹H NMR (300
MHz, CD₂Cl₂) δ: 7.64-7.62 (m, 4H), 7.59-7.56 (m, 2H), 4.28 (s, 8H); ¹³C NMR (75MHz, CD₂Cl₂) δ: 137.0, 135.8, 131.2, 130.2, 45.0; HRMS (EI⁺) calcd. for C₁₆H₁₄Cl₄ ([M]+): 345.9853, found: 345.9850.

Typical Procedure for The Synthesis of Complexes 10a-e:

Synthesis of 2,2',6,6'-Tetrakis-boraneyldiphenylphosphanyl)methyl]-biphenyl (10a)

\[
\begin{array}{c}
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\text{Ph}_2\text{P} \\
\text{BH}_3
\end{array}
\]

\[
\begin{array}{c}
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\text{Ph}_2\text{P} \\
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\begin{array}{c}
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\text{Ph}_2\text{P} \\
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\[
\begin{array}{c}
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\text{Ph}_2\text{P} \\
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\text{Ph}_2\text{P} \\
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\]

\[
\begin{array}{c}
\text{BH}_3 \\
\text{Ph}_2\text{P} \\
\text{BH}_3
\end{array}
\]

n-BuLi (5.28 mL, 2.5 M in hexane, 13.2 mmol) was added dropwise to a cooled (-78 °C) solution of diphenylphosphine (2.32 mL, 13.2 mmol) in THF (10 mL). After stirring for 10 min, the reaction mixture was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was cooled to -78 °C and tetrachloride 9 (1.05 g, 3 mmol) in THF (10 mL) was added dropwise. After addition, the reaction mixture was allowed to warm to r.t. slowly and stirred overnight. The reaction mixture was cooled to 0 °C and a cold solution of BH₃ (1.0 M in THF, 132 mL, 132 mmol) was added dropwise. The mixture was allowed to warm to r.t. and stirring was continued for 4 h. The reaction mixture was cooled to 0 °C and water (20 mL) was added carefully to quench the excess BH₃. (Caution: gas generated vigorously upon the addition of water). The volatile material was removed under vacuum and CH₂Cl₂ (50 mL) and water (50 mL) were added to the residue. The mixture was stirred for 10 min until all of the residue dissolved. The
organic phase was separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 × 25 mL). The combined organic phase was washed with brine (50 mL) and dried with Na$_2$SO$_4$. The solvent was removed under reduced pressure to obtain an off-white solid. EtOAc (10 mL) was added to the crude solid and the resulting suspension was stirred for 30 min and filtered. The residue was washed with cold EtOAc (2 × 5 mL) to give the pure borane-protected title compound 10a as a colorless solid (2.5 g, 73.8 %). $^1$H NMR (300 MHz, CDCl$_2$) δ: 7.58-7.52 (m, 16 H), 7.45-.39 (m, 8 H), 7.36-7.31 (m, 16H), 7.03-6.97 (m, 2H), 6.87-6.84 (m, 4H), 3.16 (d, $J$ = 13.4 Hz, 8H ), 1.53-0.75 (bs, 12H); $^{13}$C NMR (75MHz, CD$_2$Cl$_2$) δ: 133.1, 132.5 (d, $J$ = 9.1 Hz), 131.5, 131.3, 130.6, 130.4, 129.2 (d, $J$ = 9.9 Hz), 127.5, 30.2 (d, $J$ = 30 Hz); $^{31}$P NMR (146 Hz, CD$_2$Cl$_2$) δ:15.2. HRMS (ES$^+$) calcd. For C$_{64}$H$_{66}$NaP$_4$B$_4$ ([M+Na]$^+$): 1025.4385, found: 1025.4431.

**Typical Procedure for The Synthesis of Ligand 2a-e:**

**Synthesis of 2,2',6,6'-Tetrakis-[(diphenylphosphanyl)-methyl]-biphenyl (2a)**

![Chemical Structure](image_url)

Compound 10a (501 mg, 0.5 mmol) was added in portions to a solution of DABCO (448 mg, 4 mmol) in toluene (10 mL) under nitrogen atmosphere. The resulting suspension was stirred for 30 min at RT then slowly heated to 60 °C. Stirring was continued for 6 h at 60 °C then the reaction mixture was cooled to RT and additional toluene (10 mL) was added. The diluted solution was charged on a short silica gel column
by cannula and eluted with toluene (40 mL) under nitrogen atmosphere. The solvent was removed under vacuum to give the desired ligand 2a as a white solid (376 mg, 79.4%). The ligand was stored under nitrogen due to its air sensitivity. $^1$H NMR (300 MHz, CDCl$_2$) $\delta$: 7.32-7.22 (m, 40H), 6.91-6.86 (m, 2H), 6.76-6.74 (m, 4H), 3.24 (s, 8H); $^{13}$C NMR (75MHz, CD$_2$Cl$_2$) $\delta$: 139.6, 139.3, 137.1, 137.0, 133.5, 133.3, 128.9, 128.7, 127.4, 35.0 (d, $J = 25.8$ Hz); $^{31}$P NMR (146 Hz, CD$_2$Cl$_2$) $\delta$: -15.3. HRMS (ES$^+$) calcd. for C$_{64}$H$_{55}$P$_4$ ([$M$+H]$^+$): 947.3254, found: 947.3237.

Complex 10b: Prepared according to the typical procedure by using di(3,5-difluorophenyl)phosphine (7.9 g, 30.6 mmol), nBuLi (2.5 M in hexane, 12.3 mL, 30.6 mmol), tetrachloride 9 (2.4 g, 6.9 mmol), and BH$_3$ (1.0 M in THF, 300 mL, 300 mmol). Yield: 5.1 g (64.1%) as white solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.25 - 7.14 (m, 16H), 7.12 (t, $J = 8.0$ Hz, 2 H), 6.99 - 6.92 (m, 16 H), 6.74 (d, $J = 8.0$ Hz, 4H), 3.34 (d, $J = 13.6$ Hz, 8H), 1.45 - 0.52 ppm (br s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 163.1 (ddd, $^1$J = 254.2, $^2$J = 16.1 Hz, $^3$J = 11.8 Hz), 138.1, 133.5 (dt, $^1$J = 52.3, $^2$J = 8.0 Hz), 132.1, 129.9 (dd, $^1$J = 4.6, $^2$J = 1.5 Hz), 128.8, 115.1 (ddd, $^1$J = 18.5, $^2$J = 10.5, $^3$J = 8.6 Hz), 107.8 (t, $J = 24.9$ Hz), 29.8 ppm (d, $J = 33.6$ Hz); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: -105.2 ppm; $^{31}$P NMR (161 MHz, CDCl$_3$) $\delta$: 19.0 ppm; HRMS (ESI): $m/z$: calcd for C$_{64}$H$_{50}$B$_4$F$_{16}$P$_4$ ([$M$]+): 1290.298; found: 1290.296.

Ligand 2b: Prepared according to the typical procedure by using complex 10b (1.3 g, 1.0 mmol) and DABCO (0.896 g, 8.0 mmol). Yield: 901 mg (73.0%) as white solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.10 (t, $J = 7.6$ Hz, 2 H), 6.85 - 6.72 (m, 28 H), 3.21 ppm (s, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 141.8, 138.3 (d, $J = 24$ Hz), 135.6 (dd,
$^{1}J = 5.5, ^{2}J = 3.2$ Hz), 130.9, 129.1, 128.9 (q, $J = 2.8$ Hz), 128.5, 128.2, 125.3, 115.4 (td, $^{1}J = 14, ^{2}J = 7.3$ Hz), 105.0 (t, $J = 24.8$), 35.0 ppm (q, $J = 5.8$ Hz); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: -108.1 ppm; $^{31}$P NMR (146 MHz, CDCl$_3$) $\delta$: -11.1 ppm; HRMS (ESI): $m/z$: calcd for C$_{64}$H$_{39}$F$_{16}$P$_{4}$ ([M+H]+): 1235.8634; found: 1235.8623.

Complex 10c: Prepared according to the typical procedure by using di($p$-trifluoromethylphenyl)phosphine (6.5 g, 20.3 mmol), nBuLi (2.5 M in hexane, 8.1 mL, 20.3 mmol), tetrachloride 9 (1.6 g, 4.6 mmol), and BH$_3$ (1.0 M in THF, 200 mL, 200 mmol). Yield: 4.9 g (68.9%) as white solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.84 (t, $J = 6.4$ Hz, 16H), 7.66 (d, $J = 6.4$ Hz, 16H), 6.99 (t, $J = 7.6$ Hz, 2 H), 6.63 (d, $J = 7.6$ Hz, 4H), 3.52 (d, $J = 13.6$ Hz, 8 H), 1.40-0.60 ppm (br s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 138.6 (t, $J = 7.7$ Hz), 134.3 (d, $J = 52.3$ Hz), 133.3 (qd, $^{1}J = 33.6, ^{2}J = 2.3$ Hz), 132.5 (d, $J = 9.5$ Hz), 129.7 (d, $J = 1.5$ Hz), 128.5, 126.0 (dd, $^{1}J = 9.8, ^{2}J = 3.8$ Hz), 123.3 (q, $J = 270.1$ Hz), 29.6 ppm (d, $J = 33.7$ Hz); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: -63.4 ppm; $^{31}$P NMR (161 MHz, CDCl$_3$) $\delta$: 16.2 ppm; HRMS (ESI): $m/z$: calcd for C$_{72}$H$_{58}$B$_4$F$_{24}$P$_4$ ([M]+): 1546.3478; found: 1546.3466.

ligand 2c: Prepared according to the typical procedure by using complex 10c (773 mg, 0.5 mmol) and DABCO (0.448 g, 4.0 mmol). Yield: 559 mg (75.0%) as white solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.42 (d, $J = 7.6$ Hz, 16H), 7.21 (t, $J = 18.2$ Hz, 16 H), 6.97 (t, $J = 7.6$ Hz, 2 H), 6.70 (d, $J = 7.6$ Hz, 4H), 3.20 ppm (s, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 142.7 (t, $J = 26.4$ Hz), 138.6, 136.2 (d, $J = 10.8$ Hz), 133.2 (d, $J = 30.0$ Hz), 131.4 (q, $J = 33.5$ Hz), 128.7 (d, $J = 4.5$ Hz), 128.2, 125.4 (t, $J = 3.1$ Hz), 123.8 (q, $J = 270.2$ Hz), 34.9 ppm (dd, $^{1}J = 10.2, ^{2}J = 5.4$ Hz); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: -62.9
ppm; $^{31}$P NMR (146 MHz, CDCl$_3$) $\delta$: -14.1 ppm; HRMS (ESI): m/z: calcd for C$_{72}$H$_{47}$F$_{24}$P$_4$ ([M+H]$^+$): 1491.2245; found: 1491.2237.

Complex 10d: Prepared according to the typical procedure by using di(p-methylphenyl)phosphine (9.1 g, 42.8 mmol), nBuLi (2.5 M in hexane, 17.2 mL, 42.8 mmol), tetrachloride 9 (3.4 g, 9.7 mmol), and BH$_3$ (1.0 M in THF, 200 mL, 200 mmol) in THF (250 mL). Yield: 7.6 g (71.2%) as white solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.48 (t, $J = 9.2$ Hz, 16H), 7.13-7.08 (m, 16 H), 6.97 (t, $J = 7.8$ Hz, 2 H), 6.85 (d, $J = 7.8$ Hz, 4H), 3.17 (d, $J = 13.6$ Hz, 8H), 2.35 (s, 24 H), 1.15-0.85 ppm (br s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 141.1 (d, $J = 2.2$ Hz), 138.8 (d, $J = 7.7$ Hz), 132.9, 132.0 (d, $J = 9.4$ Hz), 129.7 (d, $J = 5.0$ Hz), 127.9, 127.4, 127.1, 29.9 (d, $J = 35$ Hz), 21.3 ppm; $^{31}$P NMR (161 MHz, CDCl$_3$) $\delta$: 13.3 ppm; HRMS (ESI): m/z: calcd for C$_{72}$H$_{82}$B$_4$P$_4$ ([M]+): 1114.5722; found: 1114.5739.

ligand 2d: Prepared according to the typical procedure by using complex 10d (1.10 g, 1.0 mmol) and DABCO (0.896 g, 8.0 mmol). Yield: 825 mg (78.0%) as white solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.16 (t, $J = 7.2$ Hz, 16H), 7.04 (d, $J = 7.2$ Hz, 16H), 6.90 (t, $J = 7.6$ Hz, 2H), 6.78 (d, $J = 7.6$ Hz, 4H), 3.16 (s, 8 H), 2.33 ppm (s, 24H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 138.1, 136.8 (d, $J = 11.4$ Hz), 135.9 (d, $J = 14.5$ Hz), 133.0 (d, $J = 20.1$ Hz), 129.4 (d, $J = 10.1$ Hz), 129.0 (d, $J = 6.8$ Hz), 128.0 (d, $J = 5.1$ Hz), 126.9, 34.7 (d, $J = 14.1$ Hz), 21.3 ppm; $^{31}$P NMR (146 MHz, CDCl$_3$) $\delta$: -16.4 ppm; HRMS (ESI): m/z: calcd for C$_{72}$H$_{71}$P$_4$ ([M+H]$^+$): 1059.4501; found: 1059.4522.

Complex 10e: Prepared according to the typical procedure by using di(m-trifluoromethylphenyl)phosphine (8.3 g, 25.7 mmol), nBuLi (2.5 M in hexane, 10.3 mL, 25.7 mmol), tetrachloride 9 (2.0 g, 5.8 mmol), and BH$_3$ (250 mL, 1.0 M in THF, 250
mmol). Yield: 6.0 g (67.1%) as white solid; $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ: 7.98 (d, $J = 10.8$ Hz, 8 H), 7.88 (t, $J = 8.8$ Hz, 8 H), 7.75 (t, $J = 8.8$ Hz, 8 H), 7.57 (td, $^1J = 7.6$ Hz, $^2J = 2.0$ Hz, 8 H), 6.96 (t, $J = 8.0$ Hz, 2 H), 6.62 (d, $J = 8.0$ Hz, 4 H), 3.47 (d, $J = 13.2$ Hz, 8 H), 1.51-0.60 ppm (br s, 12H); $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$) δ: 139.3 (t, $J = 7.8$ Hz), 135.9 (d, $J = 7.8$ Hz), 132.5 (d, $J = 66.2$ Hz), 132.2 (qd, $^1J = 32.7$, $^2J = 10.9$ Hz), 130.6, 130.4 (d, $J = 9.3$ Hz), 130.3 (dd, $^1J = 6.0$, $^2J = 1.0$ Hz), 129.4 (dt, $^1J = 11.9$, $^2J = 3.6$ Hz), 129.2 (t, $J = 4.3$ Hz), 128.8, 121.4 (qd, $^1J = 270.2$, $^2J = 1.7$ Hz), 30.6 ppm (d, $J = 33.8$ Hz); $^{19}$F NMR (376 MHz, CD$_2$Cl$_2$) δ: -63.2 ppm; $^{31}$P NMR (161 MHz, CD$_2$Cl$_2$) δ: d=17.0 ppm; HRMS (ESI): m/z: calcd for C$_72$H$_58$B$_4$F$_{24}$P$_4$ ([M]$^+$): 1546.3478; found: 1546.3463.

Ligand 2e: Prepared according to the typical procedure by using complex 10e (1.5 g, 1.0 mmol) and DABCO (0.896 g, 8.0 mmol). Yield: 954 mg (64.0%) as white solid; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.58 (t, $J = 6.4$ Hz, 8 H), 7.48 (d, $J = 3.2$ Hz, 8 H), 7.42-7.33 (m, 16 H), 6.98 (t, $J = 7.6$ Hz, 2 H), 6.64 (d, $J = 7.6$ Hz, 4 H), 3.28 ppm (s, 8 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 150.6, 139.4 (d, $J = 8.0$ Hz), 138.4, 136.0 (d, $J = 74.4$ Hz), 134.1, 131.0 (q, $J = 32.7$ Hz), 129.5 (d, $J = 20.8$ Hz), 129.0, 128.6, 128.1, 127.9, 125.8 (d, $J = 3.7$ Hz), 121.4 (q, $J = 397.7$ Hz), 35.4 ppm (dd, $^1J = 33.8$, $^2J = 5.1$ Hz); $^{19}$F NMR (376 MHz, CDCl$_3$) δ: -62.8 ppm; $^{31}$P NMR (146 MHz, CDCl$_3$) δ: -13.1 ppm; HRMS (ESI): m/z: calcd for C$_{72}$H$_{47}$B$_4$F$_{24}$P$_4$ ([M+H]$^+$): 1491.2245; found: 1491.2233.

Optimized Procedure for The Synthesis of Ligand 2f:

Synthesis of 2,2’,6,6’-tetracarboxylicacid biphenyl (11):
To pyrene (6.00 g, 29.7 mmol) in CH$_2$Cl$_2$ (120 mL) was added MeCN (120 mL) and water (180 mL). To the resulting biphasic solution was added NaIO$_4$ (60 g, 280 mmol) followed by Ru(III)Cl$_3$ (240 mg, 1.16 mmol). The solution warmed somewhat as the reaction began but was not vigorous. The reaction was run overnight (~16 h) with stirring and was filtered to give a yellow solid. The mixed solid (tetraacid/NaIO4) was extracted with acetone (750 mL) and the acetone was filtered to yield a yellow solution. Upon evaporation the product was identified as a mixture of the desired tetraacid and the corresponding dianhydride. The crude product was ground to a fine powder and was refluxed for 1 h in CH$_2$Cl$_2$ before being filtered hot. The tetraacid was collected as a white powder (7.5 g, 75% yield). $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$: 12.4 (br s, 4 H), 7.96 (d, $J = 7.6$ Hz, 4H), 7.45 (t, $J = 7.8$ Hz, 2H). $^{13}$C NMR (75.4 MHz, DMSO-d$_6$) $\delta$: 167.49, 142.07, 132.33, 131.82, 126.49.

**Synthesis of biphenyl 2,2',6,6'-tetracarboxylicacid chloride (12):**

The tetraacid 11 (2.5 g, 7.5 mmol) was suspended in CH$_2$Cl$_2$ (150 mL) and cooled to 0 °C. Then, thionyl chloride (100 mL, excess) and DMF (0.2 mL, catalytic) were
added. The suspension was allowed to warm to room temperature under N₂. After 1 h the suspension was warmed to reflux until a homogenous solution developed (about 4 h). After another hour at reflux the orange solution was concentrated to dryness, dry toluene was added, and the solution was concentrated again to yield a yellow solid. After evacuation on a high vacuum for 1 h the compound (2.9 g, 95%) appeared pure by NMR. 

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \] \( \delta \): 8.57 (d, \( J = 8.1 \text{ Hz} \), 4H), 7.81 (t, \( J = 8.1 \text{ Hz} \), 2H).

**Synthesis of 2,2',6,6'-Tetrakis(hydroxymethyl) biphenyl (7):** To a solution of LiAlH₄ (3.04 g, 80.0 mmol) in anhydrous THF (160 mL) was added dropwise a solution of biphenyl 2,2',6,6'-tetracarboxylicacid chloride 12 (2.4 g, 6.0 mmol) in THF (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then was warmed to reflux and stirred for 48h. After cooled to room temperature, H₂O (4.0 mL) was added dropwise at 0 °C (Caution: vigorous gas evolved). An aqueous solution of NaOH (40 mL, 15 % w/w) was added and stirred for 1 h. The organic layer was separated and the aqueous phase was extracted with ethyl ether (150 mL) for three times. The combined organic extracts were dried over MgSO₄. Removing the solvent under vacuum afforded 7 as a white solid (1.2 g, 73 % yield, pure enough for next use). 

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \] \( \delta \): 7.45-7.42 (m, 4H), 7.36-7.31 (m, 2H), 4.72 (bs, 4H), 3.97 (s, 8H); 13C NMR (75MHz, CDCl₃) \( \delta \): 137.8, 132.7, 126.0, 125.2, 59.8.

**Synthesis of 2,2',6,6'-Tetrakis-bromomethyl-biphenyl (9):** To a solution of 2,2',6,6'-Tetrakis(hydroxymethyl) biphenyl 7 (1.0 g, 3.6 mmol) in CH₂Cl₂ (20 mL) was added thionyl chloride (4.0 mL) and DMF (0.1 mL, catalytic) at 0 °C. The reaction
mixture was allowed to warm to room temperature and then was warmed to reflux and stirred for 24 h. After cooled to room temperature, the reaction mixture was concentrated to dryness. Pure product was obtained by recrystallization from CH$_2$Cl$_2$/hexanes as a white solid (1.1 g, 90% yield).

**Synthesis of 2f:** To a solution of di(3,5-ditrifluoromethylphenyl)phosphine (3.68 g, 8.03 mmol) in THF (20 mL) was added $n$-BuLi (3.21 mL, 2.5 M solution in hexane, 8.03 mmol) dropwise at -78 °C. After stirring for 4 hs, a solution of 9 (0.64 g, 1.83 mmol) in THF (8 mL) was added dropwise. After addition, the reaction mixture was allowed to warm to room temperature slowly and stirred overnight. The resulting solution was concentrated under vacuum to around 5 mL, and anhydrous ether (40 mL) was added. The solution was washed with degassed water (3 × 10 mL). The organic phase was dried over Na$_2$SO$_4$. The filtrate was concentrated in vacuum to around 3 mL to form white precipitate. The solid was collected and washed with cold ether (2 × 4 mL) to afford pure ligand 2f (3.01 g, 82%) as white solid. [All operation are carried out under inert atmosphere, all liquid are transferred with cannula.] $^1$H NMR (400 MHz, C$_4$D$_8$O): $\delta$ = 8.10 (s, 8 H), 7.77 (s, 16 H), 7.21 (t, $J$ = 7.2 Hz, 2 H), 6.88 (d, $J$ = 7.2 Hz, 4 H), 3.61 (s, 8 H); $^{13}$C NMR (100 MHz, C$_4$D$_8$O): $\delta$ = 141.8 (d, $J$ = 12.4 Hz), 139.4, 137.4, 134.0, 133.3 (q, $J$ = 35.1 Hz), 130.2 (d, $J$ = 19.1 Hz), 124.8, 124.3 (q, $J$ = 271 Hz), 36.3 (d, $J$ = 24.1 Hz); $^{19}$F NMR (376 MHz, C$_4$D$_8$O): $\delta$ = -64.3; $^{31}$P NMR (146 MHz, C$_4$D$_8$O): $\delta$ = -10.0; HRMS (ESI): $m/z$ = 2035.1231, calcd. for C$_{80}$H$_{39}$F$_{48}$P$_4$ ([M+H]$^+$): 2035.1236; found: 2035.1231.
Crystal Data and Structure Refinement for Ligand 1:

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Refinement method Full-matrix least-squares on $F^2$

Data / restraints / parameters 10255 / 1355 / 576

Goodness-of-fit on $F^2$ 1.000

Final R indices [$I>2\sigma(I)$] $R1 = 0.0552$, $wR2 = 0.1301$

R indices (all data) $R1 = 0.0638$, $wR2 = 0.1367$

Largest diff. peak and hole 0.924 and -0.756 e.Å$^{-3}$

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**General Procedure for the Linear-selective Isomerization-hydroformylation of Internal Olefins with Tetraphosphoramidite Ligand 1**

To a 2 mL vial with a magnetic stirring bar was charged ligand 1 (3 μmol) and Rh(acac)(CO)$_2$ (1 μmol in 0.1 mL of toluene). The mixture was stirred for 5 min. Then 2-octene (10 mmol) was added followed by decane (0.1 mL) as internal standard. The reaction mixture was transferred to an autoclave. The autoclave was purged with nitrogen for three times and subsequently charged with CO (5 bar) and H$_2$ (5 bar). The autoclave was then heated to 100 °C (oil bath). After 1 h, the autoclave was cooled in icy water and the pressure was carefully released in a well ventilated hood. The reaction mixture was immediately analyzed by GC.

**General Procedure for the Linear-selective Hydroformylation of Terminal Olefins with Tetraphosphoramidite Ligand 1**
To a 2 mL vial with a magnetic stirring bar was charged ligand 1 (0.6 μmol in 0.2 mL toluene) and Rh(acac)(CO)$_2$ (0.2 μmol in 0.2 mL toluene). The mixture was stirred for 5 min. Then 1-octene (2 mmol) was added followed by decane (0.1 mL) as internal standard. Additional toluene was added to bring the total reaction volume to 1 mL. The reaction mixture was transferred to an autoclave. The autoclave was purged with nitrogen for three times and subsequently charged with CO (10 bar) and H$_2$ (10 bar). The autoclave was then heated to 100 °C (oil bath). After 1 h, the autoclave was cooled in icy water and the pressure was carefully released in a well ventilated hood. The reaction mixture was immediately analyzed by GC.

**General Procedure for the Regioselective Hydroformylation of Terminal Olefins with Tetraphosphine Ligands 2a-f**

To a 2 mL vial with a magnetic stirring bar was charged tetraphosphine ligand 2 (4 μmol) and Rh(acac)(CO)$_2$ (1 μmol in 0.1 mL toluene). The mixture was stirred for 5 min. Then 1-octene (2 mmol) was added followed by decane (0.1 mL) as internal standard. Additional toluene was added to bring the total reaction volume to 1 mL. The reaction mixture was transferred to an autoclave. The autoclave was sealed and purged with nitrogen for three times and subsequently charged with CO (10 bar) and H$_2$ (10 bar). The autoclave was then heated to 140 °C (oil bath). After 1 h, the autoclave was taken out of the oil bath and cooled in icy water. The pressure was carefully released in a well ventilated hood. The reaction mixture was immediately analyzed by GC.
References


Chapter 5

Electron-Donating, Rigid $P$-Stereogenic Bisphospholane Ligands for Highly
Enantioselective Rh-Catalyzed Asymmetric Hydrogenations

5.1 Introduction

Development of chiral phosphorus ligands has drawn intensive interest and been
widely applied to a large number of transition metal-catalyzed asymmetric reactions.\(^1\)
This partially attribute to the good coordination ability of phosphorus ligands to various
metal centers, and more importantly, the efficient ability to define an asymmetric
environment around the metal centers with chiral phosphorus ligands. In addition, in
many cases, phosphorus ligands are is feasible to systematical modification, which may
lead to fine-tuning of the reaction selectivity.\(^2\)

Catalytic asymmetric hydrogenation has been well developed and proven to be a
practical and efficient method for the synthesis of enantiomerically enriched products in
pharmaceutical, agrochemicals, animal health and material industries.\(^3\) Hundreds of chiral
phosphorus-containing ligands have been developed since the seminal work by
Knowles\(^4\), Horner\(^5\) and Kagan.\(^6\)

Especially the excellent enantioselectivities have been obtained by using $P$-
stereogenic phosphorus ligands, such as DIPAMP\(^7\) reported by Knowles and DuPhos\(^8\)
developed by Burk and co-workers in DuPont, which have directed significant amount of
efforts to extend both designs and the applications of this ligand class (Figure 5-1). One of the major reasons is because the chiral environment induced by the ligands is close to the transition metal centers. Some elegant $P$-stereogenic ligands include Bis$P^*$ (1,2-bis(alkylmethylphosphino)ethane)$^9$ and miniphos (1,2-bis(alkylmethylphosphino)methane) developed by Imamoto group,$^{10}$ as well as trichickenfootphos (tertbutylmethylphosphino-di-tert-butylphosphinomethane) reported by Hoge and co-workers in Pfizer (Figure 5-1).$^{11}$ These ligands provide excellent enantioselectivities in asymmetric hydrogenation, especially for the challenging prochiral tetra-substituted olefins. However, the development of $P$-stereogenic ligands is still limited owing to difficulty with synthesizing them. Most of the current synthetic methods rely on chiral induction from (-)-sparteine (only one enantiomer is available), resolution or chiral HPLC separation. The quest for $P$-Stereoic ligands that can be prepared easily and with high enantioselectivity, reactivity and broad substrate scope is of great importance in catalysis. In this chapter, we reported a new highly electron-donating and conformationally rigid $P$-stereogenic bisphospholane ligand 1 (named ZhangPhos; Figure 5-1) where both enantiomers can be synthesized conveniently. High enantioselectivities and reactivities have been achieved at room and elevated temperature in rhodium catalyzed hydrogenation of various functionalized alkene derivatives.
5.2 Results and Discussion

5.2.1 Design and Synthesis of ZhangPhos 1

Our research group has ever reported a $P$-stereogenic ligand $1$, TangPhos, which were proven an excellent ligand in Rh and Pd-catalyzed asymmetric hydrogenation for a wide variety of substrates. More recently, many other groups found that TangPhos exhibited the highest enantioselectivities for diverse transition-metal-catalyzed asymmetric reactions such as arylcyanation and alkylation of imidazoles at high
temperatures. However, only one enantiomer of TangPhos ($1S,1'S,2R,2'R$-1) is readily available owing to the requisition of enantioselective deprotonation using (-)-sparteine/nbutyllithium. Later on, we introduced another $P$-stereogenic phosphorus ligand 2, DuanPhos, with both enantiomers being available. But the synthesis of DuanPhos requires resolution using D- or L-dibenzoyl tartaric acid in the final step and its electron-donating ability is not as strong as that of TangPhos. The wide applications of TangPhos and DuanPhos encourage us to develop a more synthetically practical and conformationally rigid $P$-stereogenic bisphospholane scaffold.

We envisioned that the distinctive chair configuration of chiral cyclohexane ring could provide efficient enantioselective induction for deprotonation and result in a pure single enantiomer in the oxidative coupling product. Therefore, we designed a $P$-stereogenic ligand, ZhangPhos, based on cyclohexane bisphospholane backbone. The two five-membered phospholane rings in the backbone of ZhangPhos are believed to restrict the conformational flexibility and lead to high enantioslectivity. It is envisioned that the electron-rich bis(trialkylphosphane) structure contributes to the high reactivity. In addition to the excellent enantioselective induction, the two chiral cyclohexane rings on the backbone are expected to further benefit the electron-donating ability and conformational rigidity of ZhangPhos (Figure 5-2).
ZhangPhos was synthesized in a straightforward manner in five steps which are illustrated in Scheme 5-1. From a commercially available chiral source, (1S,2S)-1,2-cyclohexanedicarboxylic acid (4) (it was afforded by chemical resolution of racemic trans-1,2-cyclohexanedicarboxylic acid with optically pure α-phenylethylamine in our experiment17), chiral diol 5 was obtained quantitatively by reduction with lithium aluminium hydride. According to a known procedure,18 chiral diol 5 was cyclized with thionyl dichloride and followed by oxidation with ruthenium(III) trichloride and sodium periodate to afford Cyclic sulfate 6 in 88 % yield. Reaction of 6 with lithiated tert-butylphosphane, and subsequent in situ protection with sulfur powder afforded enantiomerically pure phosphane sulfide 7 (>99 % ee was determined by HPLC on a chiral stationary phase). A oxidative homocoupling mediated by [Fe(acac)3] in the presence of sec-butyllithium provided the C2-symmetric bisphosphane sulfide 8 in 50 % yield, along with recovered starting material 7 (25%). Desulfuration of 8 with
hexachlorodisilane\textsuperscript{12a} afforded ligand 3, \((1S,1'S,2R,2'R,3aS,3'aS,7aS,7'aS)-ZhangPhos\), as a white crystalline solid in 90\% yield.

Scheme 5-2: The Synthesis of ZhangPhos.

The absolute configuration of 8 was determined by X-ray crystallographic analysis of a single crystal of it which was cultured by solvent diffusion from hexane to ethyl acetate solution. The X-ray analysis of the crystal was displayed by ORTEP drawing in Figure 5-3. The configuration of precursor of ZhangPhos exactly matches our expectation and indicates that the chiral cyclohexane backbone provides an efficient enantioselective induction for the deprotonation and oxidative coupling.
The key step in this synthetic route is the enantioselective oxidative coupling of compound 7. The high regio- and enantioselectivities were believed to attribute to the chiral chair configuration of cyclohexane moiety which makes one of the four methylene hydrogen atoms in the phospholane ring distinct from the other three. This point was proved by a careful 2-D HSQC NMR analysis. As illustrated in Scheme 5-3, all proton and carbon atoms are assigned by $^1$H NMR, $^{13}$C NMR, $^{13}$C DEPT NMR and 2-D HSQC NMR. On the $^1$H NMR spectrum, the chemical shift of H$_a$ on C$_1$ atom is located in lower field than the other three methylene protons. With the help of molecular simulation of compound 7, it was deduced that the C$_1$-H$_a$ bond is parallel to the P=S bond. The weak reaction between H$_a$ and S made the signal of H$_a$ shift to low field. This parallel structure can also facilitate the formation of a four-membered ring for the following deprotonation.
intermediate (Scheme 5-3). This specific feature of compound 7 contributed the high selectivity of coupling step. The oxidative coupling was carefully optimized. We screened different base (nBuLi, sBuLi, and tBuLi), oxidant (CuCl2, FeCl3, Fe(acac)3) as well as the deprotonation temperature (-78 °C, -40 °C, -20 °C) and obtained the current best reaction condition.

Scheme 5-3: 2-D HSQC NMR Analysis of Compound 7.

5.2.2 Asymmetric Hydrogenation with ZhangPhos

ZhangPhos was then applied in the rhodium-catalyzed hydrogenation of various prochiral alkene derivatives. The cationic Rh complex, [Rh(ZhangPhos)(nbd)]BF4 (9; nbd=3,5-norbornadiene), was prepared and used directly as the catalyst precursor. α-(Acylamino)acrylic acids and esters were hydrogenated under very mild conditions (in
methanol at room temperature under 20 psi of H\textsubscript{2} for 12 h).\textsuperscript{20} Full conversions and extremely high enantioselectivities (>99 % ee exclusively) were obtained in the hydrogenation of both \(\alpha\)-(acylamino)acrylic acids and their ester derivatives (Table 5-1). The catalyst can tolerate a wide array of substituted phenyl rings and thio ring (Table 5-1, entries 5-12), as well as the \(N\)-benzoyl derivative (Table 1, entry 14). To further evaluate the catalytic efficiency of the Rh–ZhangPhos system in asymmetric hydrogenation, methyl 2-acetamido-3-(4-fluorophenyl)acrylate (10g) was hydrogenated using 0.002 mol % of complex 9 under the same reaction conditions. In this way, (S)-11g was obtained with >99 % ee in quantitative yield within 4 hours, thus indicating a high turnover number (TON = 50000) and a high turnover frequency (TOF = 12 500 h\textsuperscript{-1}) for the Rh-ZhangPhos catalyst.

A variety of \(\alpha\)-arylenamides 12 were also hydrogenated with the Rh-ZhangPhos catalyst to afford enantiomerically pure amides (Table 5-2). Ee values of more than 99 % were achieved exclusively in the hydrogenation of enamides 12, regardless of the substituents on the phenyl ring (Table 5-2, entries 1-8). Rh-ZhangPhos also showed tolerance to the \(E/Z\) mixture of trisubstituted enamides and gave excellent enantioselectivity (Table 5-2, entries 10 and 11). High turnover (10 000) was also obtained in the hydrogenation of \(N\)-(1-(4-bromophenyl)vinyl)acetamide (12g) with >99 % ee in quantitative yield. These results are among the best reported to date.
Table 5-1: Rhodium-catalyzed Asymmetric Hydrogenation of α-(Acylamino) Acrylic Acids and Esters.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>10</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>ee [%]\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>H</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>n-Pr</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>i-Pr</td>
<td>H</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>Ph</td>
<td>H</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>Ph</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>p-FC\textsubscript{6}H\textsubscript{4}</td>
<td>H</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>p-FC\textsubscript{6}H\textsubscript{4}</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>p-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
<tr>
<td>9</td>
<td>i</td>
<td>p-CF\textsubscript{3}C\textsubscript{6}H\textsubscript{4}</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
<tr>
<td>10</td>
<td>j</td>
<td>m-BrC\textsubscript{6}H\textsubscript{4}</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
<tr>
<td>11</td>
<td>k</td>
<td>o-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
<tr>
<td>12</td>
<td>l</td>
<td>2-thienyl</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
<tr>
<td>13</td>
<td>m</td>
<td>2-naphthyl</td>
<td>H</td>
<td>&gt;99</td>
</tr>
<tr>
<td>14\textsuperscript{c}</td>
<td>n</td>
<td>Ph</td>
<td>Me, N-Bz</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The reactions were carried out at room temperature under 20 psi of H\textsubscript{2} in MeOH for 12 h with 9 (1 mol %) as the catalyst precursor. Conversions were 100 %. \textsuperscript{b} The ee values
were determined by GC or HPLC on a chiral stationary phase using a Chiralsil-VAL III FSOT or a Chiralcel OJ column, respectively. The ee values of the acids were determined for the corresponding methyl ester by treatment with TMSCHN$_2$. The absolute configurations of the products were determined as $S$ by comparison of the retention times of two enantiomers with reported data.$^{12a}$ The protecting group on N was changed from Ac to Bz for this reaction. Bz=benzoyl, TMS=trimethylsilyl.

The two chiral cyclohexane rings fused on the phospholane rings are expected to make ZhangPhos more conformationally rigid and electron-donating than TangPhos. It has been demonstrated that high rigidity and a well-defined structure are beneficial to achieving high enantioselectivity.$^3$ As shown in Table 5-3, Rh-ZhangPhos gave higher or comparable enantioselectivities compared to Rh-TangPhos in the hydrogenation of another three types of prochiral olefins: enol acetates 14 (Table 5-3, entries 1-5), $\beta$-(acetylamino)acrylates 15 (Table 5-3, entries 6-10), and itaconic acid derivatives 16 (Table 5-3, entries 11 and 12). For the hydrogenation of aromatic enol acetates, which serves as an alternative to direct hydrogenation of ketones, increase of enantioselectivity was observed by using Rh-ZhangPhos as the catalyst, especially for 14b (from 92 % to 98 % ee; Table 5-3, entry 2). $\beta$-(Acetylamino) acrylates remain challenging substrates for asymmetric hydrogenation, which can form nonnatural chiral $\beta$-amino acids. With Rh-ZhangPhos, the hydrogenation of both $E$ and $Z$ isomers of $\beta$-(acetylamino)acrylates derivatives 15 gave high enantioselectivities (from 92 % to more than 99 % ee). In particularly, for ortho-substituted substrate 15e, a significant increase in
enantioselectivity (from 74 % to 92 % ee) was obtained with the Rh-ZhangPhos complex (Table 5-3, entry 10).

Table 5-2: Rh-catalyzed Asymmetric Hydrogenation of α-Arylenamide.\(^{a}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>12</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>ee [%](^{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>Ph</td>
<td>H</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>m-MeC(_6)H(_4)</td>
<td>H</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>m-MeOC(_6)H(_4)</td>
<td>H</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>m-BrC(_6)H(_4)</td>
<td>H</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>p-MeC(_6)H(_4)</td>
<td>H</td>
<td>&gt;99</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>p-ClC(_6)H(_4)</td>
<td>H</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>p-BrC(_6)H(_4)</td>
<td>H</td>
<td>&gt;99</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>p-MeOC(_6)H(_4)</td>
<td>H</td>
<td>&gt;99</td>
</tr>
<tr>
<td>9</td>
<td>i</td>
<td>2-naphthyl</td>
<td>H</td>
<td>&gt;99</td>
</tr>
<tr>
<td>10</td>
<td>j</td>
<td>Ph</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
<tr>
<td>11</td>
<td>k</td>
<td>p-CF(_3)C(_6)H(_4)</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

\(^{a}\) See footnotes of Table 5-1. For the E/Z ratio of 12j-k, see reference [21]. \(^{b}\) The ee values were determined by GC or HPLC on a chiral stationary phase using a Chiral Selective 1000 or a Chiralcel OD-H column, respectively. The absolute configurations of
the products were determined as \( S \) by comparison of their retention times of two enantiomers with reported data.\(^{12a}\)

Table 5-3: Rh-catalyzed asymmetric hydrogenation of enol acetates, \( \beta \)-(acetylamino)acrylates and itaconic acid derivatives.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>ee [%]</th>
<th>ZhangPhos</th>
<th>TangPhos</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>14a Ar = Ph</td>
<td>97(S)</td>
<td>96(R)(^c)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>14b Ar = ( p )-FC(_6)H(_4)</td>
<td>98(S)</td>
<td>92(R)(^c)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>14c Ar = ( p )-ClC(_6)H(_4)</td>
<td>97(S)</td>
<td>97(R)(^c)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>14d Ar = ( p )-NO(_2)C(_6)H(_4)</td>
<td>( &gt;99)(S)</td>
<td>99(R)(^c)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>14e Ar = 2-naphthyl</td>
<td>99(S)</td>
<td>97(R)(^c)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>15a R = Me (( E ))</td>
<td>( &gt;99)(S)</td>
<td>( &gt;99)(R)(^d)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>15b R = Me (( Z ))</td>
<td>97(S)</td>
<td>97(R)(^d)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>15c R = Et (( E ))</td>
<td>( &gt;99)(S)</td>
<td>( &gt;99)(R)(^d)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>15d R = Ph (( Z ))</td>
<td>95(R)</td>
<td>94(S)(^d)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>15e R = ( o )-MeC(_6)H(_4) (( Z ))</td>
<td>92(R)</td>
<td>74(S)(^d)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>16a R = Me</td>
<td>( &gt;99)(R)</td>
<td>99(S)(^c)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>16b R = H</td>
<td>( &gt;99)(R)</td>
<td>99(S)(^c)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) See footnotes of Table 5-1. Solvent was ethyl acetate for 14, THF for 15, and 16.\(^b\) The ee values were determined by GC or HPLC on a chiral stationary phase (see references
The absolute configurations of the products were determined by comparison of the retention times of two enantiomers with reported data.\(^{c}\) Data from reference [12c].\(^{d}\) Data from reference [12b].

In asymmetric catalysis, the enantioselectivity generally decreases at high temperature as a result of the ligand flexibility. The conformationally rigid cyclohexane rings were expected to reduce the flexibility of ZhangPhos and sustain high enantioselectivity at high temperature. Indeed, some preliminary results of hydrogenations requiring higher temperature showed that ZhangPhos has better tolerance to high temperature than TangPhos. As shown in Table 5-4, the hydrogenation of N-aryl \(\beta\)-enamino esters 17\(^{12d}\) (Table 5-4, entries 1-3) and aryl imino esters 18\(^{12e}\) (Table 5-4, entries 4 and 5), where a temperature of 50 °C was needed, Rh-ZhangPhos delivered higher enantioselectivities than Rh-TangPhos. It is expected that ZhangPhos will have promising applications in asymmetric catalytic processes, which require elevated temperature.\(^{13a,b}\)
Table 5-4: Rh-catalyzed asymmetric hydrogenation of N-aryl β-enamino esters and α-aryl imino esters.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>ee [%]</th>
<th>ZhangPhos</th>
<th>TangPhos</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17a Ar= Ph, R= Me</td>
<td>93(+)</td>
<td>91(-)(^c)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>17b Ar= Ph, R= Et</td>
<td>96(+)</td>
<td>95(-)(^c)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>17c Ar= p-FC(_6)H(_4), R= Et</td>
<td>98(+)</td>
<td>96(-)(^c)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>18a Ar= Ph</td>
<td>97(R)</td>
<td>95(S)(^d)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>18b Ar= o-MeOC(_6)H(_4)</td>
<td>97(+)</td>
<td>95(-)(^d)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) For 17, the reactions were carried out at 50 °C in TFE under 6 atm of H\(_2\) for 18 hours with 9 (1 mol %). For 18, the reactions were carried out at 50 °C in CH\(_2\)Cl\(_2\) under 50 atm of H\(_2\) for 24 hours with 9 (1 mol %). Conversions were 100 %. \(^b\) The ee values were determined by GC or HPLC on a chiral stationary phase (see references [12d,e]). \(^c\) Data from reference[12d]. \(^d\) Data from reference [12e]. PMP = para-methoxyphenyl, TFE = trifluoroethanol.

5.2.3 Ligand 19, Isomer of ZhangPhos

In the oxidative coupling of compound 7, we noticed that there was a minor product (20) which showed single peak on \(^{31}\)P NMR spectrum and has higher polarity than compound 7 and 8 (being eluted out later than 7 and 8 in column chromatography).
Although its yield is only 12 %, we determined its structure based on NMR spectra and single crystal X-ray analysis. The configuration was displayed by ORTEP drawing in Figure 5-4, which showed that compound 20 has same stereochemistry on every chiral center as compound 8, except a much bigger <PCCP dihedral angle that makes the two phosphorus atoms located on the two side of the new formed C-C bond.

Figure 5-4: ORTEP Representation of compound 20 at 50% Probability for The Drawing of Thermal Ellipsoids (Solvents and Hydrogen Atoms Are Omitted for Clarity).

Compound 20 was then transformed into ligand 19 by deprotection of sulfur (Scheme 5-4). The application of ligand 19 in rhodium-catalyzed asymmetric hydrogenation of a series of representative aforementioned substrate showed that ligand 19 provide almost no enantioselectivity for asymmetric hydrogenation. This is probably due to the big <PCCP dihedral angle which does not allow the two phosphorus atoms
coordinate to the same rhodium center and makes ligand 19 act as a monophosphorus ligand.

Scheme 5-4: The Synthesis of Ligand 19.

5.3 Conclusion

In conclusion, we have designed and developed a new highly electron-donating, $P$-stereogenic bisphospholane ligand 3 (ZhangPhos), which can be synthesized practically and highly enantioselectively from a commercially available chiral reagent. ZhangPhos exhibited extremely high enantioselectivities (up to 99 % ee) and reactivities (up to 50 000 TON) for rhodium-catalyzed hydrogenation of a wide range of functionalized olefin derivatives. Compared to TangPhos and DuanPhos, better or comparable enantioselectivities were achieved with ZhangPhos, which suggests that the chiral cyclohexane rings on its backbone make the ligand more conformational rigid. Especially, better enantioselectivities obtained at high temperature makes ZhangPhos a promising ligand for high temperature asymmetric catalysis. Further studies to optimize the synthesis of ZhangPhos and explore its application in diverse asymmetric catalytic reactions are ongoing.
Experimental Section

**General Methods:** All reactions and manipulations that were sensitive to moisture or air were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. Solvents were dried with standard procedures and degassed with N₂. Column chromatography was performed using 200-400 mesh silica gel supplied by Natland International Corp. Thin-layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. \(^1\)H, \(^{13}\)C, and \(^{31}\)P NMR spectra were recorded in CDCl\(_3\) or CD\(_2\)Cl\(_2\) on Bruker Avance 400 MHz spectrometers or Varian Mercury 500 MHz FT-NMR spectrometer. Optical rotation was obtained on a Perkin-Elmer 341 MC polarimeter. HRMS were recorded on a Thermo LTQ Orbitrap hybrid mass spectrometer. GC analysis was carried out on Hewlett-Packard 7890 gas chromatography using chiral capillary columns. HPLC analysis was carried out on Agilent 1200 series.

**Preparation of (1S,2S)-1,2-cyclohexanedicarboxylic acid (4):**

To a solution of (S)-1-phenylethylamine (6.80 g, 56.0 mmol) in EtOH (80 mL) was added racemic *trans*-1,2-cyclohexanedicarboxylic acid (9.60 g, 55.8 mmol) at -78 °C. A white slurry was formed, which was filtered off after warming to room temperature. This solid was recrystallized from hot EtOH/toluene (1:1, 160 mL) three times. The product thus obtained was dissolved in 1 N aq. HCl and extracted three times with Et\(_2\)O (200 mL). The combined organic layers were dried over MgSO\(_4\) and evaporated under reduced pressure, affording the enantiomerically pure dicarboxylic acid 4 as colorless crystals (1.87 g, 19 % yield, >99 % ee). For the ee determination, a sample
of 4 was converted into the dimethyl ester by treatment with an solution of TMSCHN$_2$ and analyzed by GC on a 25 m Supelco $\beta$-Dex CB column. $[\alpha]^{20}_D = +18.2$ (c 1.00, acetone), lit.17 $[\alpha]^{20}_D = +18.3$ (c 1.00, acetone).

**Synthesis of (1S,2S)-Cyclohexane-1,2-diyldimethanol (5):**

To a suspension of LiAlH$_4$ (6.76 g, 178.0 mmol) in anhydrous THF (150 mL) was added (S, S)-4 (12.25 g, 71.2 mmol) in portions at 0 °C. The mixture was stirred at room temperature overnight and then heated at 60 °C for 5 h. The reaction was cooled to r.t. and quenched with H$_2$O (10 mL) slowly at 0 °C (Caution: vigorous gas evolved). An aqueous solution of NaOH (40 mL, 15 % w/w) was added and stirred for 1h. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (150 mL) for three times. The combined organic extracts were dried over Na$_2$SO$_4$. Removing the solvent under vacuum afforded (S, S)-5 as a white solid (9.85 g, 98 % yield, pure enough for next use). $[\alpha]^{24}_D = -21.7$ (c = 1.2, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 4.09 (s, 2H), 3.61 (dd, $J = 10.9$, 6.4 Hz, 2H), 3.53 (dd, $J = 10.9$, 6.4 Hz, 2H), 1.75-1.73 (m, 2H), 3.61 (dd, $J = 16.8$, 1.6 Hz, 2H), 1.35-1.31 (m, 2H), 1.27-1.22 (m, 2H), 1.08-1.03 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 67.8, 44.6, 29.9, 26.1 ppm.

**Synthesis of (5aS,9aS)-octahydrobenzo[e][1,3,2]dioxathiepine 3,3-dioxide (6):**

To a solution of (S, S)-5 (5.16 g, 35.8 mmol) and triethylamine (19.95 mL, 143.2
mmol) in 120 mL of CH₂Cl₂ was added thionyl chloride (3.94 mL, 53.7 mmol) dropwise at 0 °C. The resulting dark brown solution was stirred at 0 °C for 1 h. The reaction was then quenched with water (30 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was passed a short silica gel plug (CH₂Cl₂ as eluent) to afford crystalline crude cyclic sulfite (6.61 g, 34.7 mmol). The crude product was dissolved in a mixture of acetonitrile, chloroform and water (50, 50, 75 mL respectively). NaIO₄ (11.50 g, 53.7 mmol) and RuCl₃·xH₂O (120 mg) were added at 0 °C. After vigorous stirring at 0 °C for 1.5 h, the reaction mixture was added brine (75 mL) and filtered. The organic layer of the filtrate was separated. The aqueous layer was washed with CH₂Cl₂ (50 mL) twice. The combined organic layers were dried over Na₂SO₄ and concentrated. The resulting solid residue was purified by passing through a short silica gel plug (CH₂Cl₂ as eluent) to give (S, S)-6 as a white solid (6.47 g, 88%).

\[ \alpha_{24}^D = +64.6 \ (c = 1.1, \ CHCl_3) \]

$^1$H NMR (400 MHz, CDCl₃) $\delta$: 4.30 (dd, $J = 12.0, 9.6$ Hz, 2H), 4.10 (dd, $J = 12.0, 2.4$ Hz, 2H), 1.91-1.82 (m, 2H), 1.78-1.68 (m, 2H), 1.65-1.62 (m, 2H), 1.40-1.26 (m, 2H), 1.06-0.96 (m, 2H); $^{13}$C NMR (100 MHz, CDCl₃) $\delta$: 75.6, 44.0, 27.4, 25.5 ppm; HRMS (ESI): m/z: calcd for C₈H₁₄O₄NaS ([M+Na]⁺): 229.0510; found: 229.0505.

Synthesis of (3aS,7aS)-2-(tert-butyloctahydro-1H-isophosphindole 2-sulfide (7):

![Chemical Structure]
To a mixture of \textit{tert}-butyl phosphine solution (24.48 mL, 20 \% v/v in octane, 30.0 mmol) and THF (80 mL) was added \textit{n}-BuLi (12.0 mL, 2.5 M in hexane, 30.0 mmol) dropwise at -78 °C. The resulting yellow solution was allowed to warm to r.t. and stirred for 1 h. The reaction mixture was then cooled back to -78 °C and was added a solution of (\textit{S}, \textit{S})-6 (6.19 g, 30.0 mmol) in THF (50 mL) dropwise. The resulting solution was allowed to warm to r.t. and stirred for 4 h. After being cooled to -78 °C again, \textit{n}-BuLi (12.0 mL, 2.5 M in hexane, 30.0 mmol) was added dropwise. The reaction mixture was warmed to r.t. and stirred overnight. After being quenched with degassed water (5.0 mL), sulfur powder (1.44 g, 45 mmol) was added as a portion. After being stirred for 2 h, the solvent was removed and the residue was dissolved in 200 mL ethyl acetate. The organic layer was washes with water (100 mL) and brine (100 mL) subsequently, and then dried over Na$_2$SO$_4$ and concentrated. The residue was passed a short alumina plug (ethyl acetate as eluent) and followed by recrystallization from hexane to give (\textit{S}, \textit{S})-7 as white crystals (5.59 g, 81\%). [\alpha]$_{24}^{24}$ = -45.2 (c = 1.0, CHCl$_3$) at > 99 \% ee; Enantiomeric excess was determined by HPLC analysis: Daicel ChiralPak AD, hexane/iPrOH = 99:1, flow rate = 1.0 mL/min, \lambda = 205 nm, t$_{major}$ = 11.4 min, t$_{minor}$ = 13.2 min; $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$: 2.53 (ddd, $J$ = 14.8, 6.8, 2.8 Hz, 1H), 2.01-1.76 (m, 7H), 1.57-1.46 (m, 1H), 1.37-1.10 (m, 14H); $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$) $\delta$: 46.8 (d, $J_{CP}$ = 3.3 Hz), 43.7 (d, $J_{CP}$ = 4.4 Hz), 38.5 (d, $J_{CP}$ = 47.1 Hz), 36.9 (d, $J_{CP}$ = 48.5 Hz), 33.7 (d, $J_{CP}$ = 14.3 Hz), 33.4 (d, $J_{CP}$ = 13.2 Hz), 33.1 (d, $J_{CP}$ = 15.6 Hz), 26.4 (d, $J_{CP}$ = 1.5 Hz), 26.3 (d, $J_{CP}$ = 1.5 Hz), 25.1 (d, $J_{CP}$ = 2.1 Hz) ppm; $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) $\delta$: 75.6 ppm; HRMS (ESI): $m/z$: calcd for C$_{12}$H$_{23}$NaPS ([\textit{M}+Na$^+$]): 253.1156; found: 253.1151.
Synthesis of (1S,1'S,2S,2'S,3aS,3'aS,7aS,7'aS)-2,2'-di-tert-butylhexadecahydro-1H,1'H-[1,1'-biisophosphindole] 2,2'-disulfide (8):

To a solution of N,N,N',N'-tetramethylethylenediamine (3.03 mL, 20.2 mmol) in Et₂O (35 mL) was added s-BuLi (14.4 mL, 1.4 M in hexane, 20.2 mmol) dropwise at -78 °C. After being stirred for 0.5 h, a solution of (S, S)-7 (3.87 g, 16.8 mmol) in toluene (25 mL) was added dropwise. The reaction mixture was then stirred at -78 °C for 5 h. A solution of Fe(acac)₃ (8.91g, 25.2 mmol) in toluene (45 mL) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 12 h. After washing with 100 mL aqueous HCl (2N) three times, the organic layer was dried over Na₂SO₄, concentrated and purified by column chromatography with ethyl acetate and hexane as eluent (1:20 v/v) to afford (1S,1'S,2S,2'S,3aS,3'aS,7aS,7'aS)-8 as white solid (1.93 g, 50.0 %). The crystalline product was obtained by recrystallization from ethyl acetate and hexane. [α]²⁴ D = -48.2 (c = 0.9, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ: 3.19 (dd, J = 12.8, 10.4 Hz, 2H), 2.57-2.54 (m, 2H), 2.02-2.00 (m, 4H), 1.87-1.76 (m, 4H), 1.64-1.52 (m, 4H), 1.34-0.86 (m, 28H); ¹³C NMR (100 MHz, CDCl₃) δ: 47.6 (t, JCP = 4.2 Hz), 42.4 (t, JCP = 2.4 Hz), 37.5 (m), 37.1 (m), 35.1 (t, JCP = 1.3 Hz), 34.6 (m), 34.4 (m), 26.7, 26.4, 26.2, 25.3 ppm; ³¹P NMR (162 MHz, CDCl₃) δ: 85.1 ppm; HRMS (ESI): m/z: calcd for C₂₄H₄₅P₂S₂ ([M+H]⁺): 459.2438; found: 459.2432.
Synthesis of $\left(1,1'S,2R,2'R,3aS,3'aS,7aS,7'aS\right)$-$2,2'$-di-tert-
butylhexadecahydro-$1H,1'1'H-1,1'$-biisophosphindole (3) (ZhangPhos):

To a solution of 8 (0.61 g, 1.33 mmol) in anhydrous degassed benzene (25 mL) was added Si$_2$Cl$_6$ (3.42 mL, 19.9 mmol) dropwise. The mixture was stirred under reflux and monitored by $^{31}$P NMR. 12h later, the solution was cooled to r.t. and added degassed aqueous NaOH solution (50 mL, 30 % w/w) in an ice bath (caution: vigorous HCl gas evolved). The resulting mixture was then stirred at 50 °C until the aqueous layer became clear (about 2 h). The aqueous layer was washed twice with degassed benzene (30 mL). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuum to around 1 mL. The solution was subjected a basic alumina plug with a mixture of Et$_2$O (10 mL) and hexanes (50 mL) as eluent under N$_2$. Concentration the resulted solution in vacuum afforded white crystalline $\left(1,1'S,2R,2'R,3aS,3'aS,7aS,7'aS\right)$-ZhangPhos (0.47 g, 90 %). $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.98-1.95 (m, 2H), 1.90-1.87 (m, 4H), 1.75-1.68 (m, 6H), 1.53-1.30 (m, 4H), 1.19-0.85 (m, 28H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 53.3 (t, $J_{CP} = 4.3$ Hz), 47.1 (m), 445.3 (t, $J_{CP} = 3.4$ Hz), 34.7, 31.9, 29.3 (t, $J_{CP} = 7.1$ Hz), 29.0 (t, $J_{CP} = 7.1$ Hz), 28.6 (t, $J_{CP} = 6.8$ Hz), 26.3, 25.9 ppm; $^{31}$P NMR (162 MHz, CDCl$_3$) δ: 11.1 ppm; HRMS (ESI): m/z: calcd for C$_{24}$H$_{45}$P$_2$ ([M+H]$^+$): 395.2996; found: 395.2991.
Preparation of Rh complex [Rh(ZhangPhos)(nbd)]BF₄ (9):

To a solution of [Rh(nbd)₂]BF₄ (67.3 mg, 0.18 mmol) in degassed THF (1 mL) at -10 °C was added a solution of (1S,1'S,2R,2'R,3aS,3'aS,7aS,7'aS)-3 (ZhangPhos) (74.6 mg, 0.189 mmol) in THF (2 mL). The resulting red solution was allowed to warm to r.t. and stirred for 15 min. The solution was concentrated to about 1 mL and then was added degassed Et₂O (12 mL) under vigorous stirring. The resulting precipitate was filtered, further washed with ether (3 x 10 mL) for three times, and dried under vacuum to afford 9 as an brown solid (79.1 mg, 65%). ¹H NMR (400 MHz, CDCl₃) δ: 5.69 (s, 2H), 5.60 (s, 2H), 4.20 (m, 2H), 2.43-2.38 (m, 2H), 2.08-2.01 (m, 4H), 1.87-1.75 (m, 8H), 1.43-1.38 (m, 2H), 1.22-0.90 (m, 30H); ¹³C NMR (100 MHz, CDCl₃) δ: 100.0, 91.0 (m), 80.4 (m), 77.2, 71.8 (m), 65.8, 55.4, 50.5, 47.5 (m), 45.4, 33.6 (m), 33.0 (m), 31.4 (m), 31.0 (m), 28.7 (m), 25.8, 25.6, 15.35 ppm; ³¹P NMR (162 MHz, CDCl₃) δ: 96.9 (d, $J_{Rh-P} = 153.3$ Hz) ppm; HRMS (ESI): m/z: calcd for C₃₁H₅₂P₂Rh ([M⁺]: 589.2599; found: 589.2587.

General Procedure for Asymmetric Hydrogenation:

In a glovebox filled with nitrogen, [Rh(ZhangPhos)(nbd)]BF₄ complex (6.7 mg, 0.01 mmol) was dissolved in corresponding solvent (10 mL). To 1 mL of this solution, the substrate (0.1 mmol for 1 mol % catalyst loading) was added. The resulting solution was then transferred into an autoclave and charged with 20 psi of hydrogen. The hydrogenation was performed at room temperature for 12 h. After carefully releasing the pressure in hood, the reaction mixture was passed through a short silica-gel plug to remove the catalyst. Enantiomeric excess were determined with the resulting solution by chiral GC or HPLC. For the hydrogenation of dehydroamino acids, the enantiomeric
excesses were measured after conversion into their corresponding methyl esters by treatment with TMSCHN$_2$ (TMS = trimethylsilyl).

**Determination of The Enantiomeric Excess of Hydrogenation Products:**

The ee values of 11a-n were determined according to reference [12a; G. Zhu, P. Cao, Q. Jiang, X. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 1799-1800].


The ee values of hydrogenation products of 14a-e and 16a-b were determined according to reference [12c].

The ee values of hydrogenation products of 15a-e were determined according to reference [12b].

The ee values of hydrogenation products of 17a-c were determined according to reference [12d].

The ee values of hydrogenation products of 18a-b were determined according to reference [12e].
Asymmetric Hydrogenation of Methyl 2-Acetamido-3-(4-fluorophenyl)acrylate (10g) with Low Catalyst Loading.

In a glovebox filled with nitrogen, [Rh(ZhangPhos)(nbd)]BF$_4$ complex (6.7 mg, 0.01 mmol) was dissolved in corresponding solvent (10 mL). 0.02 mL of this solution (0.00002 mmol) was added into a solution of 10g (0.237 mg, 1.0 mmol) in 5 mL of degassed MeOH. The resulting solution was then transferred into an autoclave and charged with 20 psi of hydrogen. The hydrogenation was performed at room temperature for 4 h. After carefully releasing the hydrogen, the reaction mixture was passed through a short silica gel column to remove the catalyst. The reaction conversion and the enantiomeric excess of product 11g were measured by chiral GC (chirasil Val-III) directly.
Molecular simulation of TangPhos, DuanPhos, ZhangPhos and their Rh complexes

The molecular simulation of TangPhos, DuanPhos, ZhangPhos and their Rh complexes was carried out on a Chem3D Pro with MM2 calculation (Minimum RMS Gradient = 0.010). The geometry of Rh atoms is defined as octahedral.

Comparing to free ligand, Rh-ZhangPhos has the least change in terms of the <PCCP dihedral angle ($\delta_{\text{PCCP}} = 23.1^\circ$). We envision that the less change in <PCCP...
dihedral angle means the less strain from ligand backbone, which make us believe that Rh-ZhangPhos complex is more stable and conformationally rigid.

**Crystal Data and Structure Refinement for Compound 8:**

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<th>Property</th>
<th>Value</th>
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<td>Empirical formula</td>
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<td>Formula weight</td>
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<td>Temperature</td>
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<td>Crystal system</td>
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<td>Unit cell dimensions</td>
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<tr>
<td></td>
<td>b = 18.1332(10) Å = 90°.</td>
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<tr>
<td></td>
<td>c = 17.2136(18) Å = 90°.</td>
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<tr>
<td>Z</td>
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<td>Density (calculated)</td>
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<tr>
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<td>F(000)</td>
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<td>Crystal size</td>
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</tr>
<tr>
<td>Theta range for data collection</td>
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<tr>
<td>Index ranges</td>
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<td>Reflections collected</td>
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Independent reflections 9817 [R(int) = 0.0284]
Completeness to theta = 32.08° 99.6 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.999 and 0.735
Refinement method Full-matrix least-squares on F^2
Data / restraints / parameters 9817 / 429 / 296
Goodness-of-fit on F^2 1.031
Final R indices [I>2sigma(I)] R1 = 0.0469, wR2 = 0.1175
R indices (all data) R1 = 0.0502, wR2 = 0.1201
Absolute structure parameter -0.02(5)
Largest diff. peak and hole 0.744 and -0.619 e.Å^{-3}

Crystal Data and Structure Refinement for Compound 20:

Empirical formula C24 H44 P2 S2
Formula weight 458.65
Temperature 100(2) K
Wavelength 0.71073 Å
Crystal system Monoclinic
Space group P2(1)
Unit cell dimensions a = 10.3337(11) Å  = 90°.
b = 12.2943(13) Å  = 107.362(2)°.
c = 10.5665(12) Å  = 90°.
Volume 1281.3(2) Å³
Z 2
Density (calculated) 1.189 Mg/m³
Absorption coefficient 0.341 mm⁻¹
F(000) 500
Crystal size 0.37 x 0.27 x 0.22 mm³
Theta range for data collection 2.02 to 32.04°.
Index ranges -15<=h<=15, -17<=k<=18, -15<=l<=15
Reflections collected 16926
Independent reflections 8577 [R(int) = 0.0144]
Completeness to theta = 32.04° 98.9 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.999 and 0.897
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 8577 / 1 / 259
Goodness-of-fit on F² 1.009
Final R indices [I>2sigma(I)] R1 = 0.0254, wR2 = 0.0641
R indices (all data) R1 = 0.0262, wR2 = 0.0645
Absolute structure parameter -0.01(3)
Largest diff. peak and hole 0.379 and -0.181 e.Å⁻³
References


(16) Molecular simulation of TangPhos, DuanPhos, ZhangPhos and their Rh complexes was carried out and discussed in experimental section.


(19) The X-ray crystallography data of compound 8 and 9 has been deposited into the Cambridge Crystallographic Data Centre (CCDC-776144). We thank Dr. Emge, T. for solving the crystal structure.

(20) This is not optimal condition. To compare with the results of TangPhos, the same reaction conditions were used.

VITA

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